Cancer Pain and the World Health Organization Analgesic Ladder

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Abstract

Introduction

This dissertation investigates the current management of cancer pain with particular emphasis on the World Health Organization analgesic ladder. This was considered necessary because published studies examining the adequacy of cancer pain control have suggested that the efficacy of the WHO ladder may have been overestimated and because the place of morphine as the 1st line opioid at Step III of the ladder has been challenged. The dissertation also investigates whether an alternative approach might be superior and further explores the patient barriers to the use of opioids.

Methods

The studies incorporated within this dissertation include an observational pain study examining pain control in 242 patients under the care of specialist palliative care teams, a systematic review and meta-analysis of 4 trials investigating oxycodone in cancer-related pain, a pilot study for a randomised controlled trial of an experimental 2-step analgesic ladder versus the traditional 3-step approach and a qualitative study exploring patients' views and concerns when offered opioids for the treatment of pain caused by cancer.

Results

The observational study showed that pain was not well controlled for the majority (79.3%: C.I. 74.1% to 84.4%); the systematic review showed that there was no difference in efficacy and tolerability between oxycodone and morphine; and the 2-step trial showed that earlier use of Step III opioids within the novel 2-step approach might result in better pain control. However, the qualitative study showed that patients associate morphine and other Step III opioids with death and therefore they reject them as useful means of controlling pain.

Conclusion

Morphine and other opioids currently remain our best means of managing pain caused by cancer, but that both professionals and patients require ongoing education, so that we can break down the barriers that still inhibit their use.

Dedication and Acknowledgements

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Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original, except where indicated by special reference in the text, and no part of the dissertation has been submitted for any other academic award. Any views expressed in the dissertation are those of the author.

SIGNED: Colette M. Reid **DATE:** 8th June 2007

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List of Abbreviations Used

BHOC Bristol Haematology and Oncology Centre

BPI Brief Pain Inventory

COREC Central Office for Research Ethics Committees

CRUK Cancer Research United Kingdom

CTA Clinical Trials Authorization

DDX Doctors and Dentists Exemption

GCP Good Clinical Practice

ISF Investigator Site File

LREC Local Research Ethics Committee

MHRA Medicines and Healthcare products Regulatory Agency

MREC Multi-centre Research Ethics Committee

R&D Research and Development

WHO World Health Organization

Chapter 1: Introduction

"The moment at which modern medicine typically states that "there is nothing more to be done", thus becomes the starting point for an emergent medicine of terminal care, central to which is the multi-faceted understanding of pain"[1] p.733

The management of pain due to cancer is perhaps one of the most important aspects of a palliative care physician's practice. This dissertation examines the pharmacological management of cancer pain, with emphasis on the World Health Organisation (WHO) analgesic ladder.[2] The introductory chapter will initially define the magnitude of the problem, discussing both the prevalence and consequences of cancer pain. The development of the analgesic ladder as an approach to be disseminated worldwide will be outlined and the evidence for its success reviewed. Factors associated with poor pain control will be discussed, along with a review of some alternative approaches to cancer pain described in the medical literature. The chapter will conclude with questions or issues raised about the current utility of the ladder, 20 years after it was first published.

1.1 The prevalence of cancer pain

Many different studies have attempted to estimate the burden of pain caused by cancer. These studies began to emerge in the 1980s, largely as a result of the efforts of John Bonica, the first President of the International Association for the Study of Pain, to highlight the clinical importance of pain management in all areas of medicine and to call for more epidemiological research in this previously neglected field.[3] [4] Initially studies attempted to both examine the prevalence of pain and to investigate whether prevalence rates differed according to disease site or stage. Daut and Cleeland[5]

examined data from 667 patients being seen at the University of Wisconsin hospital and found that pain was more frequently reported in patients with prostate or breast cancer compared to patients with cancer of the cervix or uterus and overall 33% of patients with metastatic disease had pain. A study of 208 ambulatory patients attending oncology outpatients at Albany Medical College in New York found an overall pain prevalence of 40%, but that this figure increased to 50% when considering those with metastatic disease particularly those with bone metastases.[6] Both these studies will have excluded patients who were unable to attend hospitals or clinics due to problems with pain and so may have under-estimated the problem. However, it is also possible that patients attending oncology centres are more likely to be those with difficult symptoms and so the pain prevalence may have been exaggerated. A later study attempted to eliminate such problems by trying to reach a broader group of patients by contacting a patient sample obtained from a cancer registry[7]. 536 of 591 patients approached, with lung, prostate, pancreas and cervical cancers agreed to an interview, the majority of which were conducted 6 months after initial diagnosis. 65% of these patients reported some degree of pain in the previous week. A review article by Kathy Foley in 1985 summarised the results to date and suggested that 15% of patients without metastatic disease, 33% of those with metastatic disease and 60-90% of those with advanced disease will suffer cancer pain.[8] Goudas and colleagues[9] conducted a more recent systematic review of studies investigating cancer pain prevalence, in an attempt to summarise their findings. This review retrieved 28 studies, almost half of which were conducted in the United States. Of the remaining studies, nine were conducted in Europe, one in Japan, one in South Africa and one in Taiwan. The authors report the wide range of settings, populations surveyed, populations recruited and methods used. Not surprisingly a wide range of prevalence rates was obtained. The lowest prevalence

figure was 14% recorded in a group of women with breast cancer post-mastectomy. The figure rises to as high as 73% recorded in a group of patients admitted to a specialty hospital for cancer in the United States. The authors were unable to synthesise the pain prevalence results from the individual studies retrieved, because of the heterogeneity of the studies, but conclude "that cancer pain is a substantial burden for the cancer patient" p.189. The different populations assessed and differing research settings undoubtedly account for the wide range of prevalence rates reported. There are data which indicate that factors associated with higher pain prevalence rates include the nature of the primary tumour, the presence of metastatic disease, the presence of bone metastases and the stage of disease.[10] The wide variation in prevalence rates has not excited much discussion or evaluation and authors have tended to report broad figures rather than attempt to reconcile the different estimates. For example the rates often quoted through the literature are that 30-50% of patients undergoing active treatment for a solid tumour and 70-90% of patients with advanced disease will experience pain.[10] It is not surprising then, that studies examining the prevalence of pain in populations referred to palliative care teams show higher prevalence rates, with pain often quoted as the commonest symptom at referral A large international study co-ordinated by the WHO Cancer and Palliative Care Unit in Geneva[11] found an overall pain prevalence rate of 60% at time of referral to any palliative care service. This figure is similar to the overall prevalence rate found in an English survey, where pain was present in 64% of 400 patients referred to three palliative care services in London.[12] The rates differed across each setting, with 75% of patients referred to outpatient facilities reporting pain, 63% of patients referred to hospital support teams, 62% of patients referred to hospice units and 56% of patients referred to community teams. A limitation of prevalence studies is that they inform us about the proportion of patients experiencing pain of any

severity and as such may not allow an understanding of the complexity or severity of the problem. Some studies have attempted to estimate pain severity and it seems that when this is done, pain is shown to be a significant problem to the individual with high rates of moderate to severe pain being reported. The WHO study found that the majority (51%) of the patients with pain had experienced moderate or severe pain.[11] A multi-centre study co-ordinated by the European Association for Palliative Care found that 32% of patients reporting pain had at least moderate pain.[13] A large international study co-ordinated by the Cancer Task Force of the International Association for the Study of Pain also attempted to classify the differing types and characteristics of pain.[14] They documented at least 22 different types of pain syndromes in 1095 patients. Twycross and colleagues conducted a survey of 111 patients in a palliative care service and showed that patients had a median of 3 pains.[15] Daut and Cleeland in their 1982 study also showed that when pain was present and experienced at a moderate or severe level, it significantly interfered with patients' enjoyment of life and general activity.[5] Pain due to cancer therefore represents a common, complex and challenging symptom for all involved in the care of patients with cancer and is probably the commonest symptom presented to palliative care professionals.

1.2 The importance of good pain control

Patients with pain have been shown to suffer more from other physical symptoms and are more likely to have low mood, greater anxiety and be more socially isolated.[16] Grond and colleagues reported the association between increased pain intensity and insomnia, sweating, vomiting and reduced mobility in a prospective case series of 1635 patients with cancer attending a pain relief clinic in Germany.[17] The prevalence rates of these other symptoms were greater in patients with very severe/maximal pain compared

to those with less pain (insomnia: 68% vs. 52%; sweating: 32% vs. 25%; vomiting: 30% vs. 26% and reduced mobility: 12% vs. 8%). Strang and colleagues have shown in several studies that levels of anxiety and depression are greater in patients with pain and that there is also a correlation between the severity of these symptoms and the intensity of pain.[18] [19] The studies by Strang confirmed the association with insomnia, but also demonstrated that social activities are reduced in patients with pain. The authors noted that all social activities listed in the questionnaire used for the study, including spending time on hobbies and seeing friends, were reduced if the patient experienced pain. This reduction in social activity and the effect on mood also led to an alteration in family roles because of reduced participation in activities. Patients with constant pain (as opposed to those who had some temporary relief from pain) were more likely to isolate themselves. Strang also highlights the acute and chronic nature of cancer pain and has demonstrated that because new pains often herald disease progression, the presence of uncontrolled pain leads to greater anxiety about the future for patients. Although Strang has conducted much of the work in this area, others have confirmed the association between pain and anxiety and depression[20-24] and pain and insomnia.[25] Not only do these relationships between pain and other symptoms have an impact on quality of life[26] [27] but they can also mean that exploring other psychosocial or spiritual issues or planning for a good death may be more difficult (my own observations). The importance of the psychosocial and existential components of pain were highlighted by Dame Cicely Saunders, when she introduced the concept of "total pain" illustrating pain as a multi-faceted experience, encompassing not only physiological characteristics, but having social, psychological and emotional components also.[28] However, she wrote in a letter to the BMJ in 1963[29] that "If physical symptoms are alleviated then mental pain is often lifted also"(p.746), such was her

belief in the importance of pain control. Strang also believes that the physical pain is key and that impacting on pain scores will allow a reduction in the total pain experienced.[19] Further evidence to highlight the importance of pain control to patients is considered in a qualitative study investigating the concept of dignity in the terminally ill.[30] After conducting a series of semi-structured interviews with 50 patients, the authors found that one of the three major themes to arise was that of illness-related concerns, of which control of physical symptoms was a significant feature. When asked, "what does the term dignity mean to you?" several patients made reference to the control of pain. Conversely, poorly controlled pain was seen as a threat to dignity. There is a further societal consequence of unrelieved pain. Pain represents the symptom of cancer that is most feared by patients and their families.[31] This may in part be explained by the commonly held belief that it is an inevitable and untreatable symptom. First-hand experiences of poorly controlled cancer pain will only serve to promulgate this myth. Good pain control is not simply about reducing pain scores. Its aim is to allow the patient to function physically, socially and spiritually if desired, and ultimately achieve a dignified pain-free death.

1.3 Management of cancer pain

It is impossible to consider the management of cancer pain without reference to the WHO analgesic ladder, initially designed as a practical and simple method for the treatment of cancer pain. The two are inextricably linked, such has been the success of the WHO's Cancer Pain Relief document,[2] which contained the original version of the ladder and was the result of work done by professionals involved with the WHO Cancer Pain Relief Programme. The requirements at the outset of the WHO programme were to devise a method for managing cancer pain that was simple, inexpensive and

globally acceptable, in order to serve the developing as well as the developed world and then to disseminate it worldwide in an effort to provide freedom from cancer pain for all by the year 2000.[32] The WHO ladder and approach to cancer pain relief has been remarkably successful and has become the worldwide standard for dealing with cancer pain. However, recent commentaries have questioned the continuing utility of the analgesic ladder and alternative models have been proposed.[33] The focus of this dissertation is the current utility of the ladder. However, in order to justify the questioning of the WHO ladder, it is necessary to describe its inception, subsequent field-testing and the literature describing its use in clinical practice.

1.3.1 Before the ladder

There was ample evidence that before the introduction of the analgesic ladder, cancer pain was poorly managed. Whilst some of this evidence was in the medical domain, with authors reporting the state of pain control in hospital settings,[34] a considerable amount of information about the poor state of cancer pain management is gained from the narratives of patients themselves. Throughout the 1960s and 1970s there was a growing literature written by patients and or their carers describing inadequate pain management, examples of which can be found in an article by Michelle Winslow, published in the Journal of Pain and Symptom Management in 2005.[35] She describes how "By the 1970s, the published voice of the patient was becoming more challenging" (p.29), mirroring the debates about personal freedom and autonomy that were taking place in wider society. All too often these narratives were critical of health professionals, who displayed attitudes towards analgesics that suggested prejudice against the use of opioids for moderate to severe pain (often referred to as strong opioids). Stories were told of reluctance to use morphine, with inappropriate use of

short-acting pethidine as an alternative, although some were advised that even injections of pethidine represented an "irrevocable step"(p.26). This is perhaps not a surprise. The prevailing medical opinion at the time was that morphine and other so called "strong" opioids were drugs of dependence and addiction. A paper on the pharmacological management of cancer pain,[36] written in the Journal of the American Medical Association in 1941, claimed "the use of narcotics in terminal cancer is to be condemned if it can possibly be avoided", reflecting the concerns of doctors at that time. In 1952, the WHO Expert Committee on Drug Dependence saw opioids as a risk to public health, stating that "Morphine, and especially heroin, will always produce compulsive craving, dependence and addiction in any individual...Such drugs cause individual and sociological damage and must be rigidly controlled" (p.46).[37] By the 1960s, Britain was one of the only two countries not to have banned the use of diamorphine. So pain was viewed as an inevitable and almost untreatable consequence of cancer because opioids such as morphine, the essential treatment, risked greater harm to the individual in the form of tolerance and addiction. Fortunately, in the United Kingdom through the 1960s, Cicely Saunders and the hospice movement, along with others such as the Pain Relief Unit at Oxford, began to challenge this belief. Cicely Saunders, a doctor with both nursing and social work experience had begun to spend more time with patients with cancer pain in St. Joseph's hospice in Hackney and began studies investigating its management. She continued these with Dr Robert Twycross in St Christopher's hospice when it opened in 1967. The outcome of this research was essentially that oral morphine was just as effective as diamorphine,[38] (confirmed by pharmacokinetic data which showed that diamorphine was metabolised to morphine in the blood) and so presented a useful oral analgesic. They also showed that the extra ingredients in the Brompton cocktail (a common treatment for severe cancer pain)

consisting of various combinations of chlorpromazine, alcohol, cocaine along with diamorphine or morphine, could be omitted and morphine alone used in its place. This latter finding was confirmed by Melzack and Mount in Canada.[39] This simplified the treatment of cancer pain in Great Britain, allowing the use of oral morphine, instead of relying on diamorphine by injection. Along with the introduction of controlled-release morphine, this resulted in an increase in the use of morphine in cancer pain.[40] In addition, by following a cohort of 115 patients over 7 years, Twycross was also able to challenge the idea that tolerance to opioids was inevitable, by showing that most patients were able to reach a steady dose which did not vary for months.[41] An article on the history of the hospice movement[1] describes how keeping the voice and individuality of the patient central to her focus, Dame Cicely Saunders advocated the use of regular analgesia, to prevent pain returning, and to reduce the patient's reliance on the health professional. She stated "If pain is constantly allowed to occur, each time the patient had to ask for something to relieve it. Not only does he then make it worse by his fear and tension but he is reminded of his dependence upon the drugs and the person who gives them to him." (p. 139)[42]

At the same time, research into cancer pain control in the United States of America was progressing in a different way. Ray Houde, a doctor, Ada Rogers, a research nurse and Stanley Wallenstein, a psychologist, were together conducting analgesic studies with patients in Memorial Sloan Kettering's James Ewing Hospital. This housed a large population of New Yorkers, with advanced cancer, admitted when they were too sick to remain at home. Whilst the novel design of these studies were to become the future standard for analgesic trials, their original focus was not the relief of pain from cancer, but the quest for the "ideal" analgesic i.e. a drug that would be as effective as morphine

and diamorphine, but not addictive. The original studies served mainly to provide analgesic potency equivalence ratios by comparing the efficacy of one opioid versus another within the same patient. As a consequence these studies, a pain consultation service arose, and Dr. Kathy Foley was one of the first pain fellows.

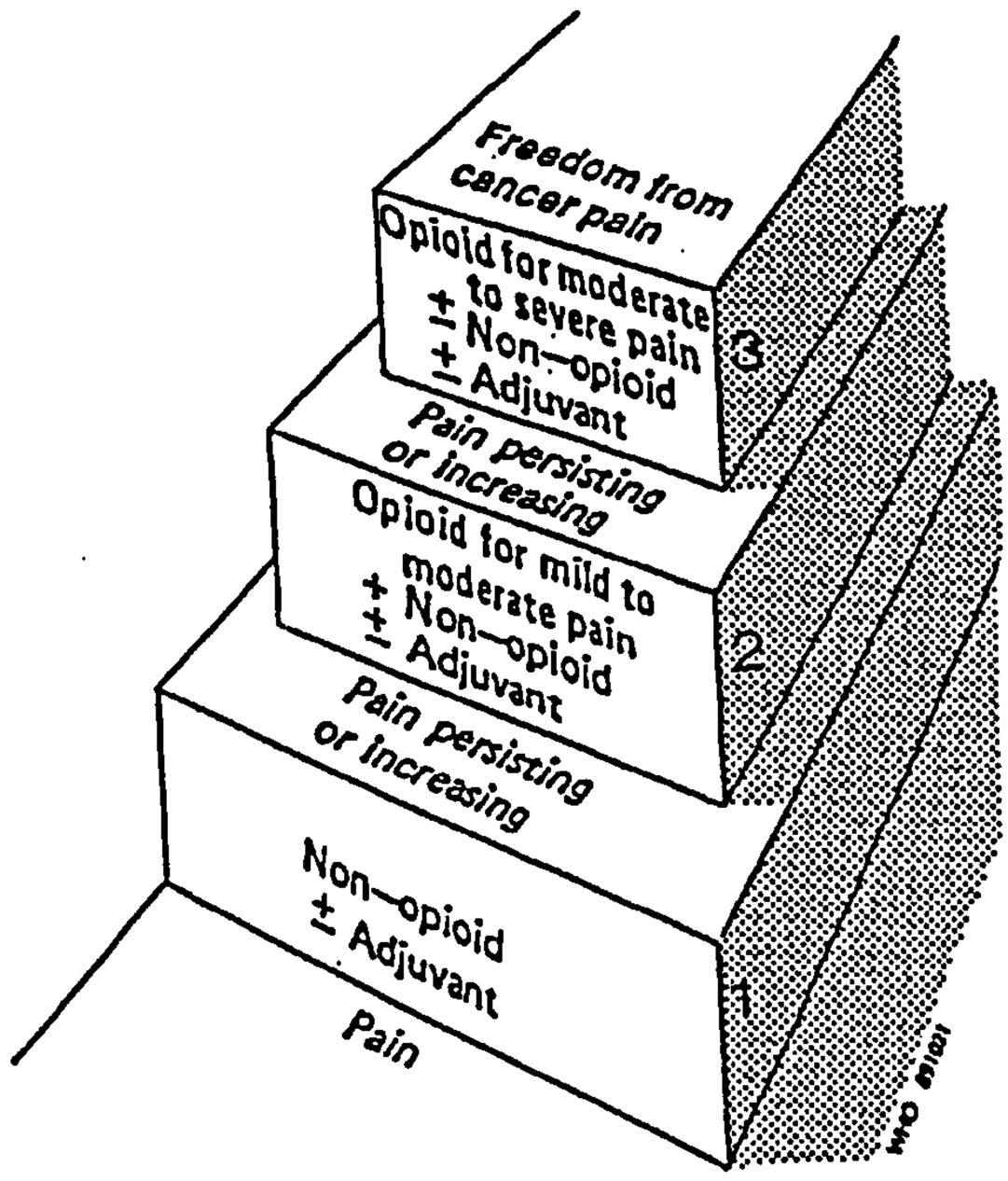
These two groups of researchers had had some opportunity to meet through the 1970s at both the International Association for the Study of Pain (IASP) conference in Florence in 1975 and the First International Symposium on Advanced Pain in Cancer in Venice in 1978. No consensus on the management of cancer pain was ever reached at these meetings, perhaps because of their differing research goals.

1.3.2 The evolution of the ladder

The impetus for reaching consensus came from the WHO itself, when, in 1982, the head of its Cancer Unit, Jan Stjernswärd, arranged an international meeting at the Villa d'Este on Lake Como, outside Milan. Stjernswärd had organized an international survey of cancer pain experiences in 1981 and the results showed that 29% of patients experiencing severe pain were receiving little or no relief.[43] Those attending the meeting included five experts in pain control, two of whom were Kathy Foley from Memorial Sloan-Kettering and Robert Twycross from St. Christopher's Hospice. Although the three of the other pain specialists present at the meeting also had experience in non-pharmacological pain-relieving interventions (John Bonica, Mark Swerdlow and Vittorio Ventafridda) it was recognised that what was required was a policy for cancer pain that was centred on drug use or a "global script"[37] (guidelines which were simple and could be easily and cheaply disseminated into both the developing and developed world). Stjernswärd's vision was one of "a simple method

that an idiot like me can know"[37] (p.49) , but providing a simple diagrammatic algorithm for the management of cancer pain was also to serve as a legitimate framework for the provision of opioids for cancer pain control. Thus, the three-step ladder, which incorporated the approach of aspirin (or non-opioid analgesic) as first-line pharmacological management of cancer pain, progressing to codeine (termed "weak" opioid) and then to oral morphine (termed "strong" opioid) as pain progresses, evolved. The main principle of the approach was that the choice of analgesic was determined by pain severity and this was clarified in the 1996 version of the ladder,[44] when the terms "weak" and "strong" were replaced by the phrases "opioids for mild to moderate pain" and opioids for moderate to severe pain" (Figure 1).

Figure 1: Diagram of the ladder



At all three steps, the use of adjuvant drugs are recommended in order to treat the adverse effects of opioids, to enhance pain relief (e.g. steroids) and to treat concomitant psychological problems e.g. depression.[2] Non-drug measures and drugs for neuropathic pain e.g. anti-depressants and anti-convulsants are also suggested, although not incorporated into the diagram.

Emphasis was also placed on the regular administration of drugs and was framed by the maxim "by the clock and by the ladder". Robert Twycross had presented this approach at the Venice meeting in 1978, emphasising the need for the use of oral opioids to be dictated by pain severity and not life expectancy. However, at this stage the views of the U.S. and the U.K. were still opposing, with the Sloan-Kettering pain team considering parenteral morphine superior to oral and remaining concerned about regular use of opioids and the clinical importance of tolerance. The 1982 meeting forced a resolution of these two stances and resulted in the publication of the ladder within the booklet "WHO Draft Interim Guidelines Handbook on Relief of Cancer Pain".[45]

Another larger meeting of experts in the management of pain due to cancer convened by the WHO was held in Geneva in 1984, two years after the original meeting. Those present at this meeting were more multi-disciplinary and multi-professional and represented 15 different countries. Data were presented by Fumikazu Takeda, reporting his successful experience of the use of the ladder in Saitama, Japan, where 97% of patients achieved acceptable pain relief (defined as > 90% pain relief as reported by the patient) by following the 1982 guidelines.[46] Those attending this second meeting endorsed the analgesic ladder and the dissemination phase began simultaneously with

further field-testing of the guidelines. The publication of the WHO booklet, Cancer Pain Relief[2] did not take place until 1986 however, two years later. This was in part due to continuing opposition to the use of morphine from some senior figures in the WHO,[37] with the chief of WHO publications suggesting the guidelines were an "attempt to spread morphine all over the world"(p.52). Once published, the guidelines were translated into many languages and worldwide programmes began to teach the importance of cancer pain control.[43]

1.3.3 Field test programme

If Stjernswärd's aim of a method that was scientifically valid was to be realised, then the efficacy of ladder had to be tested. A multi-national project was co-ordinated by the WHO collaborating centre in Milan in conjunction with the WHO collaborating Centre for Biostatistics Evaluation at Harvard University in Boston. The aims of the project were to both test the utility of the ladder by measuring the extent to which centres around the world were able to comply with the recommendations and to validate the ladder by measuring its efficacy in the treatment of cancer pain.

The project occurred in three phases. Phases I and II were designed to identify centres to assist with patient recruitment to the studies, with questionnaires sent out to 63 possible centres in 29 countries, asking about the availability of drugs for pain relief (including the specific drugs available for use at each step), the use of non-pharmacological methods for pain relief and the personnel resources, facilities and continuing care networks available to each centre. In the initial years following the first publication of Cancer Pain Relief, 35 centres around the world were employed and completed questionnaires for phases I and II. Phase III consisted of two separate

studies. Centres without prior knowledge of the guidelines were chosen to submit data for Study 1, measuring the efficacy of usual or current cancer pain management practices. Centres already knowledgeable about the guidelines were enrolled into Study 2, thereby testing the efficacy of the guidelines themselves. In total, 25 centres in 15 countries submitted results to the WHO Collaborating Centres. The protocol for both phase III studies sent to each participating centre, was clear (Appendix 1). Patients with cancer pain were to be enrolled after an initial interview recording demographic data, cancer stage and estimated prognosis, Eastern Cooperative Group (ECOG) performance status and a description of the pain and treatment modalities used. Those centres involved in testing the guidelines were given a copy of the Interim Guidelines[45] and instructions for their use. Patients were to be followed up at two weekly, then four weekly intervals until either lost to follow-up or death. Follow-up forms recorded an assessment of pain relief (a patient self-recorded linear analogue pain relief scale {Appendix 2}), pain intensity and duration, sleep hours, drug treatments for pain given since last form completed with the reason for any changes recorded, pain drug-related side effects and other pain relieving modalities. Although it appears that these initial studies were to be directly evaluated, to determine comparative efficacies of the new guidelines versus usual practice, by the time the field-testing was reported, this aim was noted to have been unrealistic. Differences existed between centres with regards to facilities and resources to the extent that the authors of the report[47] state "it would have been incorrect to treat Studies I and II as two different experimental situations" (p.455). The authors also report that it was "quite difficult to keep close feedback contacts with the participating centres" (p.457) and that "the main drawbacks found ... were in pain evaluation and appropriateness of follow-ups" (p.457). They state that the pain evaluation had to be withdrawn because it was not well understood or correctly used in

the majority of centres. These difficulties unfortunately led to high rates of excluded data, with 64% of Study I and 31% of Study II cases lost from the final analyses. In total, data from 110 patients and 261 patients were used for Study I and II respectively. Although the authors of the report write that it was not appropriate to compare the two studies, they then did so and claimed that there was a statistically significant difference between usual control of pain and the WHO guidelines in the percentage of patients with controlled pain at the fourth week follow-up period (48.5% of patients in Study I compared with 76% of patients in Study II; $p = 0.001$).[47] No significant differences were found when comparing mean sleep hours or mean pain hours in the two studies. Perhaps one of the most significant findings from the Phase III studies was that the percentage of "strong" opioids used differed greatly in the two studies (51% of patients used strong opioids in Study II compared to only 15% of patients in Study I). The authors conclude that the superiority of the WHO guidelines was explained by this finding and that it was the use of strong opioids which explained the improved results (or the reluctance to use strong opioids which explained poor cancer pain control).

1.3.4 Validation series

Following the field-testing, numerous individual centres published the results of their studies in peer-reviewed journals, which acted as another means of dissemination of the guidelines, and further validated the use of strong opioids at Step III. The first of these papers was from the Milan Collaborating Centre itself, published in Cancer in 1986, reporting data collected from 1229 patients.[48] This study is reported as being a retrospective study in the abstract, but the methods section describes a prospective method, employing nurses in both hospital and community settings to assist patients with recording pain scores. The authors suggest that the use of drugs alone provided

satisfactory analgesia in 79% of patients, but it seems that the definition of satisfactory analgesia was based on whether or not the patient required a neurolytic procedure. They comment that complete relief of pain was almost never achieved, but that pain could be maintained at a third of its pre-treatment level. They also reported on the need for management of side effects related to Step III opioids. In 1998, Walker and colleagues[49] reported on 20 patients recruited to Study II from the Royal Marsden Hospital in London. Of the 20 recruited, 13 patients obtained adequate analgesia with drug treatment alone, achieving a fall in mean pain scores from 69mm at study entry to 36mm at week 1 as measured by a 100mm visual analogue scale. 18 of the original 20 patients eventually required Step III opioids during the study period. In nine of these patients opioid doses were able to remain stable during stable disease, over time periods that ranged from 4 – 48 weeks. Seven patients provided long-term data, showing that long-term efficacy of the guidelines was good. Side effects were reported, but were managed aggressively and did not require cessation of treatment in any individual. In 1990, Schug and colleagues[50] reported the results from the Department of Anesthesiology at the University of Cologne, where 174 patients had been recruited. This retrospective study reported that about 90% of patients achieved acceptable pain relief (patient rated as either none, mild or moderate on a six-point verbal rating scale) and that this was maintained for the duration of the study (the study was continued until the death of the patient, change of therapy to parenteral medication or neurolytic procedure, or loss of contact). Over 50% of time for any patient was spent on Step III of the analgesic ladder.

1.3.5 Jaded and Browman systematic review

In 1995, a systematic review[51] of the series of studies conducted to validate the analgesic ladder was published in the Journal of the American Medical Association, and was critical of the methodology used to estimate the efficacy of the approach. The authors, Alejandro Jadad and George Browman were working at the Department of Clinical Epidemiology and Biostatistcs at McMaster University in Canada, the "home" of the emerging Evidence-Based Medicine paradigm. They used relatively novel critical appraisal and systematic review methodologies to assess the WHO ladder and validation studies. They stated that their reasons for doing so were that data emerging from recent large pain surveys still suggested that cancer patients around the world suffered inadequate pain control and that reasons proposed to explain this finding did not ever include the possibility that the ladder may not be effective. The authors conducted an exhaustive search and retrieved 14 case series studies, six of which were excluded because of either duplicate publication or insufficient reporting. The eight studies included in the review included the published data from the field-testing,[47] the published studies by Ventafridda,[48] Walker,[49] and Takeda,[52], a further Italian study translated from Tumori,[53] a paper published in the Philippine Journal of Surgical Specialties,[54] a paper reporting results from Argentina's WHO Cancer Pain Relief Programme[55] and unpublished data from the Department of Anesthesiology at the University of Cologne,[56] detailing 10-year follow-up results from use of the ladder in 2118 patients. Jadad and Browman describe the methodological limitations of the studies included in the review (short or variable follow-up periods, retrospective studies, small sample sizes and high exclusions or losses to follow-up) and are critical that no attempt was made by any study to try to compare the efficacy of the ladder with previous pain management approaches. One of their conclusions states "the evidence

provided cannot be used confidently to generate estimates of the effectiveness of the WHO ladder" (p.1872) and that "what is still unknown is the proportion of patients for whom the ladder produces satisfactory results" (p.1872). Letters in response to this article written by Marcus Reidenberg,[57] Robert Twycross[58] and Vittorio Ventafridda with Jan Stjernswärd[59] criticise the stance taken by the authors and point out that the ladder served not only as a pain management algorithm, but also as a political tool, facilitating the acceptance of opioid use. If this had been the sole aim of the ladder, then the validation studies have demonstrated by the overwhelming proportions of patients treated at Step III (the majority of whom received morphine) that the ladder has been successful. In addition, the WHO co-operated with the International Narcotics Control Board (INCB) an independent and quasi-judicial monitoring body for the implementation of the United Nations international drug control conventions, which collects data worldwide on opioid availability and consumption.[60] These data showed that in the 10 years following the introduction of *Cancer Pain Relief*, morphine consumption rose by 450% in Australia, Canada, Denmark, Iceland, Norway, Sweden, the United Kingdom and the United States, suggesting that more morphine was being used to manage pain caused by cancer.[61] The WHO booklet *Cancer Pain Relief*[2] has since been widely disseminated and translated into 17 languages. By 1995, 40 countries had developed national policies for reducing cancer pain.[61]

1.3.6 Measuring the success of the ladder

In spite of this, the worldwide applicability of the ladder has remained questionable. In 1993, 120 countries representing more than 80% of the world's population were consuming only 23% of the total morphine used in the world. Most morphine use worldwide (77%) continued to be located in the ten top countries listed above,

representing only 7% of the world's population. In addition, their effectiveness was also questionable. If the INCB data suggested that opioids were being used more often i.e. the guidelines were being followed in these countries and if the efficacy figures from the validation series were accurate, then 80-90% of patients with pain caused by cancer should have been experiencing a reduction in pain to a level that is tolerable and can allow them to function. Unfortunately, several large national pain studies conducted in some of these top ten countries have shown that this was not the case. The first of these, published in the New England Journal of Medicine in 1994 was a survey of pain and its treatment in outpatients with metastatic cancer.[62] 1308 patients out of 1427 approached, were recruited between October 1990 and September 1991 from the Eastern Cooperative Oncology Group cancer centres, community hospitals and clinics. 871 of these 1308 patient had pain (pain prevalence = 67%). 62% of patients reporting pain rated their worst pain score as 5 or greater on an 11 point numerical rating scale, a score defined a priori by the authors as substantial pain, because patients reporting this score are more likely to also report significant functional impairment.[63] The second large study was a multicentre study of cancer pain conducted throughout France and reported in the BMJ in 1995.[64] 605 patients were recruited from 20 randomly selected sites within the five regions of France. Both inpatients and outpatients were recruited. Of the 325 patients reporting pain, 69% reported their worst pain in the past week as 5 or greater. In 2000, the Scottish Clinical Resource and Audit Group of the Scottish Executive Health Department conducted a national cross-sectional survey of cancer pain control, conducted over 16 weeks.[65] Patients were recruited from different settings (acute hospitals, specialist palliative care units, community hospitals, patients' own homes and oncology centres). In total, 955 patients were recruited, of whom 646 had pain. Of these patients with pain, 49.7% had a worst pain score of 4 or greater, again

suggesting uncontrolled pain, or pain significantly interfering with function. A more recent one day pain prevalence study conducted in Norway,[66] in all hospitalised settings showed that 44% of patients with pain had a score of 5 or greater on a 0 – 10 visual analogue scale. All of these studies suggest that the analgesic ladder might not be as effective as the earlier evidence or studies propose.

Several reasons for this are possible. The critical review by Jadad and Browman[51] suggested that the analgesic ladder itself might not be as efficacious as the validation series had shown, the over-estimates of its success perhaps arising because of the poor methodological quality of the studies. Another possibility was that it was not being used correctly and that perhaps the use of morphine, although legitimised by the ladder, remained problematic because of previous cultural fears surrounding it or because of poorly tolerated or poorly managed opioid side effects that had perhaps been better managed in the validation studies.

1.4 Problems with opioids: side effects

At the original meeting in Milan in 1982, the experts agreed that the opioid of choice to be used at Step III was morphine. This was perhaps because it was available in oral formulations, and a certain aim of the ladder was to have a method that was easy to administer and oral administration would not rely on health professionals being available for each prescribed dose. It was also the opioid that had been used most in both the United Kingdom and the United States and Ray Houde had been unable to find a superior alternative in his comparison studies. In 2001, the European Association for Palliative Care endorsed the place of morphine as the "gold standard" opioid.[67] Since the introduction of the ladder, many different formulations of morphine have been

produced and marketed by pharmaceutical companies, all of which aim to improve the usefulness of morphine. Long-acting preparations (both 12-hourly and 24-hourly) were introduced in the early 1980s and their convenience encouraged the oral administration of morphine. However, one problem with morphine is its poor bioavailability, leading to an unpredictable dose-response relationship. Although all opioids require dose-titration to find the most effective dose for the individual patient with the least side effects, a very wide dose range exists for morphine because of its unpredictable but generally poor bioavailability. All opioids are associated with a wide range of side effects, some of which patients will become tolerant to (drowsiness and nausea) and some for which tolerance never develops (constipation). Side effects clearly represent a source of concern for patients and limit the use of these drugs.[68] In addition, opioid toxicity can result in sedation, hallucinations and an experience for the individual that may result in a loss of confidence with opioids. For this reason, when alternative opioids become available, it is important to consider their relative efficacy and tolerability compared to the "gold standard" morphine, to ensure its continued place as first line opioid at step III of the analgesic ladder. One such alternative, oxycodone was re-launched in 1996, having previously been used extensively in the United States as an opioid at Step II. Oxycodone has been in clinical use for almost a hundred years; its first recorded use being in Germany in 1917.[69] In Canada, the United States and Australia it was used in combination with paracetamol or aspirin as a fixed dose combination drug, whereas in Finland it had been used as the main parenteral opioid for acute pain since the 1960s. Its use in the United Kingdom was restricted to rectal preparations.[70] Ada Rogers commented on the under-utilization of oxycodone in 1991 at a time when single entity oxycodone had become available and highlighted this with a case report of successful use of oxycodone at a dose of 30mg every four hours, a dose

far greater than that which had been allowed by combination preparations.[71] Glare and Walsh were amongst the first authors to systematically examine the use of single entity oxycodone in chronic cancer pain in 1992,[72] and to subsequently call for its re-classification as an opioid for use at step III, when a dose-ranging study found it to be as efficacious as morphine. They suggested an equianalgesic ratio of 1:1 morphine to oxycodone. The main pharmacokinetic difference between oxycodone and morphine is in oral bioavailability, which for oxycodone is about 60%-90%.[73] Subsequent studies investigated its pharmacokinetic profile and its utility in randomised controlled trials in comparison with other opioids.[74-77] However, only when oxycodone was made available in controlled release preparations in 1996 did it become suitable for use in chronic cancer pain. Shortly following its introduction and indeed even recently, some reviews suggested that it may have a more favourable side effect profile than oral morphine[78-80] and so should replace it as first line opioid.[81] Levy also makes the point that oxycodone may have less associated stigma than morphine.[79] Perhaps because of the suggestion of better tolerability and the alternative name, oxycodone has been used extensively since its introduction. Data from the International Narcotics Control Board suggest that it is being used widely, especially in the United States and the United Kingdom. (**www.incb.org** and **www.doh.gov.uk**), although some of the increase in use in the United States was perhaps because of its license for use in non-cancer pain. The yearly increase in prescriptions is greater than those seen for either fentanyl or hydromorphone; the other most commonly used alternative opioids. This may be in part because of evidence suggesting that neither of these drugs offer superiority over morphine.[82] [83] Whilst it is no doubt useful to have another alternative to morphine available at Step III, because one of the options for managing persistent side effects due to morphine is opioid rotation [84](switching to an alternative opioid in the hope that a

better efficacy/side effect profile will result) it seems that an outstanding question about the superiority of oxycodone over morphine exists. If it is indeed better tolerated or more effective, then it should be considered as the drug of choice at Step III.

1.5 Problems with opioids: myths and fears

As previously stated, opioids for moderate to severe pain (morphine, oxycodone, fentanyl, hydromorphone and methadone) are the cornerstone of cancer pain management because of their place on the third step of the analgesic ladder. It is therefore unfortunate that incorrect fears exist which prevent their proper use and so threaten the utility of the ladder. Most of these myths and fears relate to the illegal use of opioids which characterizes them as drugs of abuse and addiction, hence dangerous and illicit. Because of this, they are often viewed as drugs to be avoided or delayed until absolutely necessary. Whilst anecdotal evidence of these fears is witnessed daily by professionals managing cancer pain, further evidence for their under-use is required if we are to argue that fears and myths about opioids contribute to poor pain management. This evidence can be found in studies examining either prescribing data or analgesic prescriptions at an individual level. Berger and colleagues[85] used retrospective data from a large integrated health-insurance claims database in the United States to identify over 2000 patients with metastatic cancers and examine their pharmacy claims for the 12 months prior to death. Data were available to allow them to calculate the numbers of patients receiving both long- and short-acting opioids but also to calculate the number of days for which medication had been prescribed. They also conducted a sub-group analysis of patients with bone metastases (n=717) because these are a group of patients known to experience significant pain from their cancer.[86] The percentage of patients with and without bone metastases who had no pharmacy claims

for opioids over the entire 12-month period preceding death was 13.1% and 28.8% respectively. However, as "any opioid prescription" included opioids used at Step II of the ladder and would not necessarily reflect appropriate use of Step III opioids, the study also examined claims for prescriptions of long-acting opioids. 47% of patients with bone metastases and 77% of patients without, had no pharmacy claims for long-acting opioids in their final year of life. Although this study is limited by lacking any data on pain experienced by these patients, and is sponsored by a pharmaceutical company who manufacture two of the most commonly used long-acting opioids, these data suggest that opioids have either been under-prescribed, or that prescriptions have not been filled by the patients.

Salvato and colleagues[87] provide further evidence for insufficient prescribing by examining prescribing data from the Treviso district in Northern Italy (a country with strict opioid prescribing regulations) from 1993–2000. They used WHO methodological guidelines in order to ascertain whether or not opioid prescribing was satisfactory and simultaneously conducted a questionnaire survey of the prescribing attitudes of general practitioners. A sub-group of patients who died by the end of the data collection period and so were considered to be terminally ill outpatients were used to calculate the "adequacy" of opioid prescribing. This was done by calculating the expected "Defined Daily Doses" for this population and comparing it to the number of prescribed "Defined Daily Doses". The calculated "missing" Defined Daily Doses were then compared to the expected Defined Daily Doses and this ratio used to calculate the adequacy of opioid prescribing, which was found to be only 38%. The questionnaire data revealed high rates of anxiety about opioid side effects shown by the general practitioners, with 22.8% considering opioids shortened life expectancy. These factors

may at least partly explain the under-prescribing of opioids seen in the prescribing data. Zenz and colleagues[88] examined prescribing patterns of German physicians (both general practitioners and specialists in internal medicine) when managing cancer pain and found that only 2% of 16,630 patients with a clear diagnosis of cancer (half of whom had documented metastases) had received a prescription for a Step III opioid. At the individual patient level, the two large studies in U.S.A. and France described previously[62 64] which demonstrated high levels of uncontrolled pain, also demonstrated the under-use of Step III opioids. 42% of patients in the Eastern Cooperative study and 51% of patients in the French study reporting uncontrolled pain had a negative pain management index. The pain management index is a simple calculation used to assess the suitability of pain relief medication. Pain is scored 0 – 3 (0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain) for a patient, as is their medication according to the WHO ladder (0 = no pain relief, 1 = simple analgesia, 2= Step II or opioids for mild to moderate pain and 3 = Step III or opioids for moderate to severe pain). A negative pain management index suggests under-treatment of pain. Data does therefore exist to support the anecdotal experience that opioids are under-used and that this prevents good cancer pain control.

Barriers to the proper use of opioids exist at several levels. At the institutional level, regulations intended to prevent diversion of opioids may interfere with their availability for medical use. We are fortunate in the United Kingdom, with relatively few regulations governing the prescribing of opioids. In other countries within Europe (Italy, Poland Portugal and parts of Spain) special forms must be obtained by the doctor in person from regional offices. In Austria, Germany, Portugal, Italy and Switzerland, prescription forms for Step III opioids must be completed in triplicate. There is some

evidence that these regulations inhibit the use of opioids for cancer pain, if only by causing a generally fearful attitude towards prescribing them.[89] A similar situation has arisen in the United States where illegal prescription misuse of OxyContin (sustained-release oxycodone) in the years after it was introduced for the management of chronic pain, resulted in severe restrictions placed by the Drug Enforcement Agency. These restrictions have resulted in high-profile legal cases against pain specialists, which have served as deterrents to prescribing Step III opioids for other doctors. This is in spite of Richard and Reidenberg[90] demonstrating that there was little risk for a doctor to be subject to disciplinary action for prescribing opioids for pain if the medical record showed that a doctor-patient relationship existed and the doctor was treating a painful condition.

Equally, there is much evidence that the attitudes and knowledge of the professionals managing cancer pain may represent another barrier to the appropriate use of opioids. Several studies from many different countries and cultures have confirmed that both doctors and nurses in all healthcare settings have concerns about prescribing opioids (Table 1). To provide a comprehensive literature review of these studies is beyond the scope of this dissertation, but the studies included in Table 1 demonstrate that professionals in many settings, cultures and countries have expressed concerns about prescribing opioids or have demonstrated inaccurate knowledge about their use. It is perhaps not surprising that those studies that used similar methods to allow direct comparison between professionals in separate countries demonstrate that professionals in countries with higher rates of opioid consumption seem to exhibit better knowledge and attitudes towards their use.

Table 1 (cont'd): Table of studies exploring professionals' attitudes towards prescribing opioids

MacDonald [97] 1997	Canadian physicians (2,686)	Questionnaire	Evidence for reluctance in prescribing strong opioids (not quantified)
Oneschuck [98] 1997	2nd year family medicine residents, Alberta, Canada (78)	Examination	Serious deficiencies noted in knowledge of pain management with opioids
Sjogren [99] 1996	Random sample of 10% of Danish physicians treating pain (577)	Questionnaire*	93% thought drug dependence rarely or never caused problems 78% willing to prescribe strong opioid in clinical scenario
Vainio [89] 1995	French physicians (2669)	Questionnaire*	50% willing to prescribe strong opioid in clinical scenario
Von Roenn [100] 1993	Eastern Cooperative Oncology Group Physicians (897)	Questionnaire	31% would wait until prognosis <6 months before prescribing strong opioids; 61% reluctant to prescribe opioids
Warncke [101] 1994	Norwegian physicians (306)	Questionnaire*	93% willing to prescrib e strong opioid in clinical scenario
Wells [102] 2001	Nurses (79) and doctors (22) working in surgical unit in Dundee	Questionnaire	24% concerned about addiction; 34% thought increased doses due to tolerance; 25% did not believe opioids can be used at any stage

**questionnaires similar in these studies to allow comparisons across countries*

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The ultimate barrier to opioids however, lies with the patients themselves. Several studies have documented poor adherence rates to opioid analgesics in cancer populations. Zeppetella[103] and Kingsnorth and Wilkinson [104] have demonstrated in U.K. populations that adherence to opioid analgesics is not optimal with these drugs being the most likely drugs that patients will stop taking after discharge from inpatient palliative care units. Du Pen and colleagues[105] reported that during a randomised trial of a cancer pain management algorithm in the United States, (where patients were asked to complete daily pain diaries and had frequent monitoring from the research nurses), non- adherence rates for opioids (drug ordered / drug taken ×100) were 62–72% in both the intervention and control groups and this non-adherence negatively influenced worst pain scores. Adherence rates for adjuvant analgesics were better, with rates of 74 – 84%. Within this paper the authors report that the *"study nurses, working with patients in their homes, were continuously confronted with patients' refusal to take prescribed treatments even when pain was not well controlled and there were no side effects. Most often, when patients stopped taking prescribed medication they no longer discussed pain or its treatment with their physicians"* (p.368). Because of their inability to categorize or define the issues associated with adherence, the authors amended their subsequent trial phase to include a post-study qualitative interview with participants. These interviews were reported separately[68] and are included in the review of qualitative literature on fears about opioids later in this chapter. Ferrell and colleagues[106] set out to examine the use of routine and breakthrough analgesics calculating adherence to both in a sample of 369 patients participating in a pain-education study. Prior to any intervention, only 55% of patients took the amount of regular analgesia prescribed, 38% took less than the amount prescribed and 7% took more. They also found that only 3% of patients took the actual amount of breakthrough

medication prescribed, 1% used their breakthrough more frequently than advised and 96% took less. Whilst this study is lacking in any data describing the patients' pain it adds to the evidence that adherence and in particular adherence to opioid analgesics is an important factor in pain control. Miaskowski and colleagues[107] found further evidence for poor adherence within a randomised trial of an educational intervention for pain management, when the range of adherence rates for the "around the clock" and "prn" opioid analgesics were 84.5-90.8% and 22.2-26.6% respectively.

Many studies have confirmed that patients' fears of tolerance and addiction to opioid drugs are commonplace in both cancer and non-cancer populations and so may be two reasons for this non-adherence. Carlsson and colleagues[108] in 1997 sent a 27-item questionnaire to a random selection of 100 women admitted to the gynaecological oncology department at the University Hospital of Uppsala, Sweden and to a randomly selected group of 120 healthy women obtained from a Swedish population register. Similar numbers (86 and 87) replied from each group. Whilst approximately 80% in both groups thought that cancer pain could "almost always be controlled", and over 90% in both groups thought that morphine was an effective treatment for cancer pain, 40% of women in both groups thought that the problem with pain treatment was "the addiction caused by morphine". In both groups, those with less formal education were more likely to agree with this statement. Paice and colleagues[109] found high levels of concern about tolerance (56%) and addiction (39%) in a population of 200 patients with cancer. Patients with these concerns had greater pain scores than those without (difference in pain scores not given but $p = <0.05$). Other studies supporting these findings are documented in Table 2.

Table 2: Table of studies examining patients' concerns about morphine and the implications of these concerns

Study (1st author and date)	Population (n=)	Concerns re morphine	Impact of concerns	Other results
Ward [110] 1993	Outpatients with cancer (270)	70% agree addiction a problem; 50% agree tolerance a problem	Higher mean barrier scores in patients considered under-medicated	Higher overall barrier scores associated with more pain interference with function
Carlsson [108] 1997	Women with gynaecological cancer (86) and women without cancer (87)	>40% in both groups considered morphine addictive		Pronounced formal-education related differences (those with longer education less likely to hold this belief)
Riddell and Fitch [111]1997	Inpatients (270) with cancer pain	"Concern about addiction to pain medication" was most frequently cited barrier to pain relief		Knowledge about pain relief did not correlate with pain intensity scores
Paice [109]1998	Inpatients and outpatients with cancer	Fears of tolerance (39%) and addiction (56%)	Fear of tolerance and addiction associated with worse pain scores	Fear of tolerance had a greater negative impact on pain scores than fear of addiction
Thomason [112]1998	Inpatients and outpatients (239) with cancer	30% concerned about addiction and tolerance	Fears of tolerance and addiction were a barrier to taking opioids in only 10-20%	
Lin [113] 2000	Caregivers	BQ-T	Fear of addiction/side effects/tolerance produced hesitation in administering analgesia	
Yates [114] 2002	Inpatients with cancer (114)	64% believed there is a real danger of addiction to painkillers. 42% concerned about tolerance		

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Study (1st author and date)	Patients (n=)	Concerns re morphine	Impact of concerns	Other results
Gunnarsdottir[115] 002	Patients with cancer (172)	Measured by Barriers Questionnaire (BQ)-II (validation study for updated questionnaire)	Higher BQ scores positively related to least pain scores, time spent with moderate to severe pain and under-medication (measured by Pain Management Index)	
Lai [116] 2002	Oncology in-patients (194)		Patients with less "control" beliefs had better adherence rates suggesting that a perceived benefit of using medication to control pain outweighed negative effect beliefs	
Radbruch [117] 2002	Patients with chronic malignant and non-malignant pain (60)	38% of patients using morphine had concerns about addiction		Morphine was most commonly associated with danger (n=32), pain relief, pain and side effects
Potter [118] 2003	Inpatients and outpatients with cancer (94)	Fear of addiction 76% and concerns re side effects (67%). Belief that pain equates with disease progression (71%)	Trend towards higher total barrier scores in patients with clinically significant pain, who were also more hesitant to report pain	
Lai [119] 2003	Hospitalised cancer patients with pain (361)	Development of Pain Opioid Analgesics Belief Scale-Cancer (POABS-CA)	Patients with higher negative effects beliefs about opioids have higher average pain intensity	*"The qualitative data provided a better understanding of these patients' beliefs about opioids."*

Other potential factors impacting on cancer pain control, identified by reading the literature, include fear of side effects of pain medication, worries about distracting physicians from treating the underlying malignancy, fear that pain means disease progression, the belief that pain caused by cancer is inevitable and the belief that one must be a "good patient" and so not complain of uncontrolled symptoms. Some authors have tried to quantify all of these barriers in order to assess the degree to which they affect pain management. One of the most commonly used questionnaires is the Barriers Questionnaire[110] (BQ), which was originally validated by Ward and colleagues in 1993. The questionnaire was designed to include the fears and beliefs mentioned above, with the aim of exploring the relationship between misconceptions about cancer pain and opioids with pain control and adequacy of analgesics used. In their original study, over 70% of patients agreed that addiction was a problem, and over 50% agreed that tolerance was a concern. However, only scores related to addiction were correlated with any pain score as measured on the Brief Pain Inventory, correlating with pain on average (Pearson's correlation 0.26 p = <0.01). Summed BQ scores correlated with pain interference with function (Pearson's correlation 0.36 p = <0.01). However, higher scores for all individual factors were associated with under-medication (using less than adequate analgesia for the severity of their pain). The original barriers questionnaire was amended (shortened and updated) and then re-validated in 2002.[115] BQ-II scores were found to be weakly correlated to least pain (r = 0.19, p= 0.01) and time spent in moderate to severe pain (r = 0.19, p= 0.01). The authors state that the BQ-II score was related to adequacy of analgesics being used by the study subjects, but the mean BQ-II scores were 1.42 for subjects using adequate analgesics and 1.7 for those not (p = 0.2). Not only is this result not statistically significant, but also we are not told what a clinically relevant difference in barrier scores might be. Lai and colleagues[119] in Taiwan

felt that the original Barriers Questionnaire, which had been validated for use in Taiwan (BQT), was not sensitive enough as it did not mention opioids specifically. As part of the design phase for developing their own questionnaire, the Pain Opioid Analgesics Beliefs Scale (POABS-Ca), they attempted to address patient-derived concerns, in addition to literature and professional concerns, by conducting interviews with ten patients. This led to the inclusion of categories in the scale connecting opioids to a negative disease outcome (i.e. death from cancer) and suggesting that adults should endure as much pain as possible. The authors also commented that *"The qualitative data provided a better understanding about these patients' beliefs about opioids."*(p.378) The psychometric analyses showed that the scale was valid and reliable and in addition was clinically useful (only containing 10 questions). However, subsequent use of the POABS-CA in 194 in-patients with cancer recruited from four teaching hospitals did not find a relationship between the POABS-Ca and adherence to pain medication.[116]

Perhaps one of the reasons that correlation between barrier scores and pain scores were not consistently demonstrated is that a concern about a medication may not actually prevent the medication being taken. Thomason and colleagues[112] attempted to address this question in a study looking at patient self-reports of concerns and whether or not these acted as barriers to use of analgesics. Whilst concerns about addiction, tolerance and side effects related to opioids were present in 27%, 30% and 85% of the studied population, only 17%, 10% and 18% reported that these concerns prevented them from taking their medication. Another reason that barrier scores do not correlate with pain scores may be that the areas addressed in these questionnaires have been largely professional-derived, albeit after extensive literature searches. The questionnaires may

not actually reflect real concerns of patients. In addition, studies attempting to quantify the relationship between beliefs and behaviour are limited by the reliance on patients' self-reports of behaviour, which may not be accurate. They are also limited in that only two variables have been examined: pain scores and misconceptions about cancer pain and opioids and it is likely that other factors are involved in patients' decision-making when using analgesics for cancer pain.

Perhaps because of this, others have employed qualitative methods in order to investigate the way in which concerns impact on behaviour or to explore how patients with cancer pain make their decisions to take opioid analgesics. Ersek and colleagues[68] reported the findings from the post-study interviews with patients undertaken after a randomised controlled trial of a pain management algorithm[105] (described previously). The authors had employed purposive sampling techniques to interview a combination of non-adherers and adherers and those experiencing both poor and adequate pain relief. The initial interviews asked patients to describe their decision-making processes when using pain relief, which was initially found to be too difficult a concept for them, so subsequent respondents were asked about factors that made it difficult for them to take their analgesics and factors that facilitated analgesic use. The commonest factor reported by 12/21 patients to negatively affect analgesic use was concern about side effects. Six of these 12 patients had personally experienced side effects and in three they had led to an increasing sense of fatalism or that they just had to "live with it [pain]" (p.228). Five patients were concerned about tolerance but it was not clear how they acquired this belief (although one participant had been told by her physician that an increase in transdermal fentanyl could result in not being able to provide enough analgesia "at the end"). Coward and Wilkie[120] interviewed 20 patients with cancer pain,

10 men and 10 women and asked them, amongst other questions, "how do you go about deciding to take your pain medications?" Nine of them said they took their medication as scheduled, but others talked about holding back on medication by using other manoeuvres to deal with pain, such as going to bed. Whilst fear of side effects and addiction were mentioned, others also described needing to know "what was going on" and the hope that anti-cancer treatments may have altered their pain. Pain severity and having a task that required completion were factors in deciding to take analgesics. Another qualitative study (part of a trial investigating a self-care intervention for the management of cancer pain) examined data gained from conversations between research nurses and study participants, which had been tape-recorded.[121] Content analysis of these conversations showed that fears over medication were just one aspect of obtaining good pain control and that even when patients had overcome their fears, managing pain at home was complex and included managing several symptoms simultaneously, accessing, processing and retaining information, accessing medication and managing new pains. Randall-David and colleagues[122] confirmed the complexity of cancer pain management by patients, when they reported the findings from two focus groups held with patients with the aim of elucidating factors contributing to inadequate pain management. Factors preventing adequate pain management fell into four categories which included fear (of addiction and tolerance with pain medications, of side effects and of withholding of pain medication by family members). However, attitude, values and beliefs (about stoicism, the inevitability of pain and the stigma of so-called narcotics) structural barriers (access to a physician and pain being seen as an important symptom to discuss) and behaviours (withholding information about pain in order to be a "good patient") were other influences on obtaining good pain control.

Coyle,[123] using a narrative approach examining the lived experience of terminal cancer, provides us with perhaps the most illuminating information about patients' use of opioids for cancer pain. She conducted multiple interviews with seven persons with terminal cancer until they became cognitively impaired or too unwell to participate further and employed rigorous methods to analyse the data gathered. For these seven patients, opioids were seen as both a "blessing and a burden" (p.304). They offered freedom from pain (the blessing) but also caused poorly controlled adverse effects (the burden). She describes how this changes as they became more unwell when she states, "without exception, however, as death drew near, patients saw the availability of potent opioid drugs as a blessing". She states that opioids become more acceptable as death becomes imminent, which seems to be because opioids were seen as a guarantor of a peaceful death and also perceived by some as a welcome means of hastening death. This finding, and the information from Lai and colleagues[119] about opioids being associated with a negative disease outcome (meaning death) are the only two mentions in the recent literature about opioids and death, which has instead focused on tolerance, addiction and side effects. This is surprising given that the association of opioids with death and dying is mentioned in earlier literature.[124] It is possible that methods other than questionnaires are required to elicit sensitive information such as fear of death from patients. The change in perceptions of opioids when death approaches is clearly relevant for patients with pain related to cancer and is welcomed by their health professionals. But if palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, as stated by the World Health Organization, then we cannot, and should not, wait until death is imminent to obtain good pain control. If fear of death is another obstacle to

good pain control we should try to understand why this is so and how it can be overcome.

All of the patients involved in these qualitative studies had already commenced an opioid for moderate to severe pain and were reflecting on its use. No studies have been conducted with patients with cancer pain who are considering using morphine or other step three opioids for the first time. Little is known about this from the patients' point of view, yet this "step up", from the second to third step of the ladder may represent another important issue in obtaining pain control. If a patient or indeed their health professional is reluctant to consider opioids, then the availability of several other drugs at Step II may allow procrastination i.e. another Step II drug may be offered instead of morphine being commenced.

1.6 The second to third step

This is a particular issue when considering the ladder, because some authors have considered that the second step of the ladder i.e. the addition of an opioid for mild to moderate pain such as codeine or dextropropoxyphene (until recently) to a non-opioid, which has become ineffective for pain, has limited utility.[33] This second step created an artificial distinction between Step II and Step III opioids by using the terminology "weak" and "strong" which did not reflect their pharmacology, a fact best demonstrated by the history of the use of oxycodone, outlined in the previous section. Whilst the dose of oxycodone was limited by its use in fixed-dose combinations with paracetamol it was considered suitable for use at Step II only. However, once re-launched as a single entity formulations allowing dose titration, it has been widely used at Step III. The need for the second step of the ladder at its inception was a result of the necessity to have an

approach that was applicable worldwide and most of the world did not have Step III opioids. Perhaps it would have been unthinkable to move directly to an opioid for moderate to severe pain immediately as a non-opioid became effective, given the negative associations of morphine that prevailed at that time.

In addition to the artificial pharmacological distinction made with having both Step II and Step III, there is an issue about the efficacy of adding fixed-dose opioids for mild to moderate pain to non-opioid analgesics when the latter have become ineffective. In 1995, Eisenberg and colleagues[125] published a meta-analysis of studies testing the efficacy and safety of non-steroidal anti-inflammatory drugs (non-opioid analgesics) in the management of pain caused by cancer. Their conclusions were that single or multiple doses of opioids for mild to moderate pain alone or in combination with non-opioid analgesics did not provide greater analgesia than NSAIDs alone. Other clinical studies have tended to support this finding. De Conno and colleagues[126] demonstrated in an open study involving over 900 patients starting at Step II of the analgesic ladder, that after only two weeks, over 50% of patients had needed to increase to a Step III opioid because of lack of analgesic efficacy. Several authors have also demonstrated that using Step III opioids at lower initial doses than those routinely used, produces similar pain relief to using combinations of Step II opioids with a non-opioid, without compromising tolerability.[127-129] In particular, opioid-naïve patients have been commenced on low-dose fentanyl patches (25mcg/hour),[130 131] low dose morphine (15mg in 24 hours)[132] and low dose oxycodone (10mg in 24 hours)[133] with good analgesic effect and without unacceptable toxicity or withdrawals due to side effects.

1.7 Alternative approaches

A survey of the use of opioids by specialist palliative care teams in an area in the North of England[134] showed two thirds of opioid naïve patients were commenced directly to a Step III opioid, suggesting that some professionals had adopted a two-step approach to cancer pain management. Two randomised trials of alternative approaches have been attempted.[135] [136] The first was a randomised trial of the WHO approach versus commencing Step III opioids directly.[135] Data on 92 patients were included in the final analyses from 100 enrolled. 48 patients were randomised to the WHO approach and 44 were treated directly with Step III opioids. The choice and starting dose of each opioid was decided on a per patient basis and so were not reported in the paper. Patients were followed up until death, resulting in 503 weeks of treatment being analysed for the WHO arm and 467 weeks of treatment evaluated for the experimental approach. The pain scores were analysed as change in group means rather than individual differences and the authors suggest that because 48% of patients in the traditional approach were commenced on a Step III opioid by the end of the study period, the differences between the two approaches may have been diluted. However, in spite of this, a difference of approximately 7mm on a 0-100mm pain intensity rating scale was found between the two groups, favouring the experimental approach. Side effects were reported as absolute incidences of each side effect, (each mention by patients in their study diary was considered a single episode). Only the incidence of nausea was statistically significantly higher in the experimental arm but the numbers of episodes of vomiting did not differ between the two groups. However, the paper's discussion section, surprisingly concludes that the data support the fundamental assertions of the WHO guidelines, although they then state that the guidelines may need to be modified to take into account both disease outcomes and patient-centred outcomes. When Hanks and

colleagues[137] challenged this discussion, the study authors suggested that because the patients included in the study were excluded from oncological treatment and had a short life expectancy, it would be wrong to generalise the results of the study to all patients with cancer (and thereby invalidate the WHO ladder).

A second study by Maltoni and colleagues[136] involved randomising patients to the traditional approach or to a two-step approach, omitting the second step of the ladder. Patients entering the trial had to have pain caused by cancer, have previously found a non-steroidal anti-inflammatory drug to be ineffective and have a pain score of 5-6 on a 10 cm visual analogue scale. They were then randomised to either treatment with Step II drugs until these became ineffective, when step III treatment would be initiated (WHO approach) or directly to Step III drugs (experimental approach). Only 54 patients had been recruited after 24 months, so the study was discontinued early because of poor accrual and was probably underpowered. In spite of this there was a trend for greater time spent with a pain score of 5 or less across all pains (worst, least average and now) in the experimental arm. The differences reached statistical significance for 'worst' pain.

1.8 Conclusions

It seems from the literature that we should perhaps challenge the current status quo of cancer pain management or at least accept that there remain fundamental questions about the WHO analgesic ladder. Eminent researchers have raised methodological concerns about the studies which validated the use of the ladder, calling into question its efficacy. Alternative approaches have been tried in clinical studies with promising if not conclusive results and an alternative opioid has been launched which may be

superior to morphine. Lastly, we may not fully understand the reasons why patients are reluctant to consider using Step III opioids for cancer pain, a reluctance that impacts greatly on pain management.

1.9 Outstanding questions

1. Can we accept the estimates from the WHO validation series?

Although it is widely taught that the proportion of patients in whom the ladder achieves good results is between 80 and 90%, it seems that there is growing evidence that these figures may be incorrect. The large pain prevalence studies conducted since the dissemination of the ladder certainly suggest that the proportion of patients with controlled pain is much lower, although reasons often given for the discrepancies are that the ladder is not being used appropriately, because of the problems associated with opioids. The alternative hypothesis stated by Jadad and Browman in their review, is that the methodological quality of the validation studies was poor and the accuracy of the results is questionable.

2. If we do accept the estimates from the WHO validation series, what are the reasons for pain prevalence surveys, conducted since its widespread dissemination consistently showing poor pain control?

These pain prevalence studies have often found that patients have been under-medicated, or not receiving analgesics suitable for their pain. The reasons most commonly given for this are the fears and myths that prevent the proper use of opioids. Those fears most frequently cited in the recent literature are those of tolerance and addiction that both professionals and patients assume will occur with opioids for moderate to severe pain. However, earlier reviews suggested that patients associated

opioids with death. In order to fully address patients' fears when commencing opioids, we must know what these fears are.

3. Is it too late to estimate the efficacy of the Ladder?

Although it would now be impossible to compare the efficacy of the ladder against approaches to cancer pain relief used before its dissemination, it has proved possible to conduct trials of the 3-step approach against modifications of the ladder. Whilst neither of these trials conducted to date have clearly demonstrated superiority of the newer approaches, it seems that there is room to improve the 3-step ladder. An alternative approach should be tested in a clinical trial, which will provide information about the efficacy of both the traditional and the novel approaches.

4. How do we measure efficacy?

One of the criticisms of the validation series was that different outcome measures were used to measure pain control. Ventafridda used the proportion of patients requiring a neurolytic procedure, whilst others used pain scores. Many authors currently use a 'worst' pain score of ≥ 5 to categorize poorly controlled pain, since Serlin and colleagues suggested that this score was associated with increased pain interference with function. As yet we do not know how patients define poorly controlled pain.

5. Is morphine still the gold standard opioid?

The position of morphine as the first-line opioid at the third step has remained unchallenged to date. The newer alternative, oxycodone has been suggested to be a superior opioid, with an improved side effect profile. Some studies examining its efficacy and side effect profile in comparison with morphine have proposed clinically

important differences in side effects but very few randomised controlled trials have been conducted. It may be possible to use techniques such as meta-analysis to obtain better estimates of comparative efficacy and tolerability in order to answer this important clinical question.

1.10 Aims of the dissertation

The objectives of this dissertation were to answer the outstanding questions about the current validity and utility of the ladder, by the following studies:

1. Can we accept the estimates from the WHO validation series?

In order to clarify whether or not the WHO ladder is currently achieving its aim i.e. the relief of cancer pain I decided to measure pain control in a population of patients with cancer. In an attempt to control for the impact of professionals' fears around opioids, patients under the care of professionals experienced in the use of the ladder and skilled in the use of opioids for moderate to severe pain were studied. I conducted a multi-centre pain survey and recruited patients being seen by palliative care teams in the South West of England

2. Is morphine still the gold standard opioid?

In order to examine the comparative efficacy and tolerability of the alternative opioid oxycodone, to consider if it is superior to morphine and so should replace morphine as the opioid of choice at Step III, I conducted a systematic review of studies investigating oxycodone in the management of cancer pain.

3. Is it too late to estimate the efficacy of the Ladder?

Whilst it is impossible to conduct a trial comparing the WHO ladder to previous practice because the ladder has been adopted throughout the world, it is possible to conduct a randomised trial of the three-step ladder versus a new alternative approach, such as a two-step approach (where opioids for moderate to severe pain are commenced as soon as non-opioid analgesics are no longer sufficient). This is in fact the approach

suggested by Jadad and Browman in their systematic review of the studies examining the efficacy of the ladder. Such a trial may be too difficult to conduct in a palliative care setting, because the majority of the patients seen by palliative care teams will already be using Step III opioids. Before a definitive study can be conducted, a pilot study examining the feasibility of recruitment and examining appropriate outcome measures is required. I therefore conducted a pilot study for a two-step ladder versus the three-step approach.

4. If we do accept the estimates from the WHO validation series, why do pain prevalence surveys, conducted since its widespread dissemination, consistently show poor pain control?

Previous pain surveys have shown that under-medication is a factor in uncontrolled pain. What is not known are the relative contributions of both patients' and doctors' fears of opioids, and the extent to which patients' fears of opioids are exacerbated by those of the professionals managing pain. In addition, if we are to consider an alternative approach, which would require earlier introduction of opioids in a patient's cancer journey (albeit perhaps only by a few weeks), we need to understand what this might mean to patients and whether or not they would consider such an approach acceptable. I conducted a nested qualitative study, exploring patients concerns when offered Step III opioids for the first time within the pilot study.

5. How do we measure efficacy or whether or not pain is controlled (e.g. pain scores; function; requirement for a nerve block)?

The analgesic ladder validation studies used different end-points for determining the efficacy of the ladder. However, deciding what is controlled pain is crucial if we are to

attempt to measure efficacy of pain management approaches as compared to drug-to-drug comparisons, where absolute pain scores can be used. The majority of pain surveys quote the work of Serlin and colleagues, which demonstrates that a Brief Pain Inventory worst pain score of ≥ 5 represents pain that is likely to interfere with function and so is uncontrolled pain. Very little work, however, has been conducted with patients themselves with cancer pain to clarify for research purposes what controlled pain or uncontrolled pain means to them. In order to begin to investigate this further, a single question "overall is your pain controlled?" was added to the multi-centre pain survey, in order to provide comparisons between responses to this question and worst pain scores obtained from the questionnaire.

Chapter 2: Methods

2.1 A survey of cancer pain control by South West England Palliative Care Teams

2.1.1 Study aims

1. To define the prevalence of cancer pain in patients under the care of specialist palliative care teams in the South West of England.

2. To determine the overall proportions of nociceptive, neuropathic and mixed pain types as recorded by the patient's palliative care doctor or nurse.

3. To determine the percentage of patients with poorly controlled pain defined as a "worst" pain score of ≥ 5 on an 11-point numerical rating scale (pain which is likely to interfere with function).

4. To examine the influence of demographic variables (age, sex, setting, time known to palliative care team and socio-economic deprivation) and clinical variables (ECOG performance status, primary tumour site, use of medication and frequency of breakthrough pain) on the proportion of patients experiencing a "worst" pain score of ≥ 5 on an 11-point numerical rating scale.

5. To determine the proportion of patients requiring a rotation of opioid and prime indications for this practice.

6. To determine the proportion of patients requiring anaesthetic procedures.

7. To calculate the pain management index (PMI) for each patient to determine the extent to which his/her pain is appropriately managed.

8. To compare the results of a single question; "Overall, is your pain controlled?" with the numerical rating scale measuring worst pain.

In order to explore the hypothesis that the WHO ladder may not be as efficacious or as applicable to routine clinical care as the validation series suggested, it seemed appropriate to attempt to measure the control of cancer pain in a group of patients being treated according to its principles. One of the reasons that the validation series may have over-estimated the efficacy of the WHO ladder is that the patients recruited to the validation series will have had better follow-up, more attention to side effects and were perhaps more likely to use the prescribed medication (better adherence rates) than those patients being treated in "real-world" clinical conditions. This phenomenon is well recognized and is a reason for continuing monitoring of health interventions after randomised controlled trials have shown efficacy.[138] The patients recruited to the validation series received regular follow-up. They were seen every two weeks initially and then every four weeks and were questioned about pain control and side effects from analgesic medication at each study visit. This is likely to be more intensive follow-up than is currently experienced by most patients with cancer pain and so in order to estimate the efficacy of the ladder in pragmatic or "real world" clinical settings, methods other than clinical trials must be used. It is also important to estimate pain control in community populations as well as in in-patient settings, to test the ease with which the WHO ladder can be followed by the patients themselves.[139] In order to achieve these goals, we conducted a cross-sectional survey of cancer pain control.

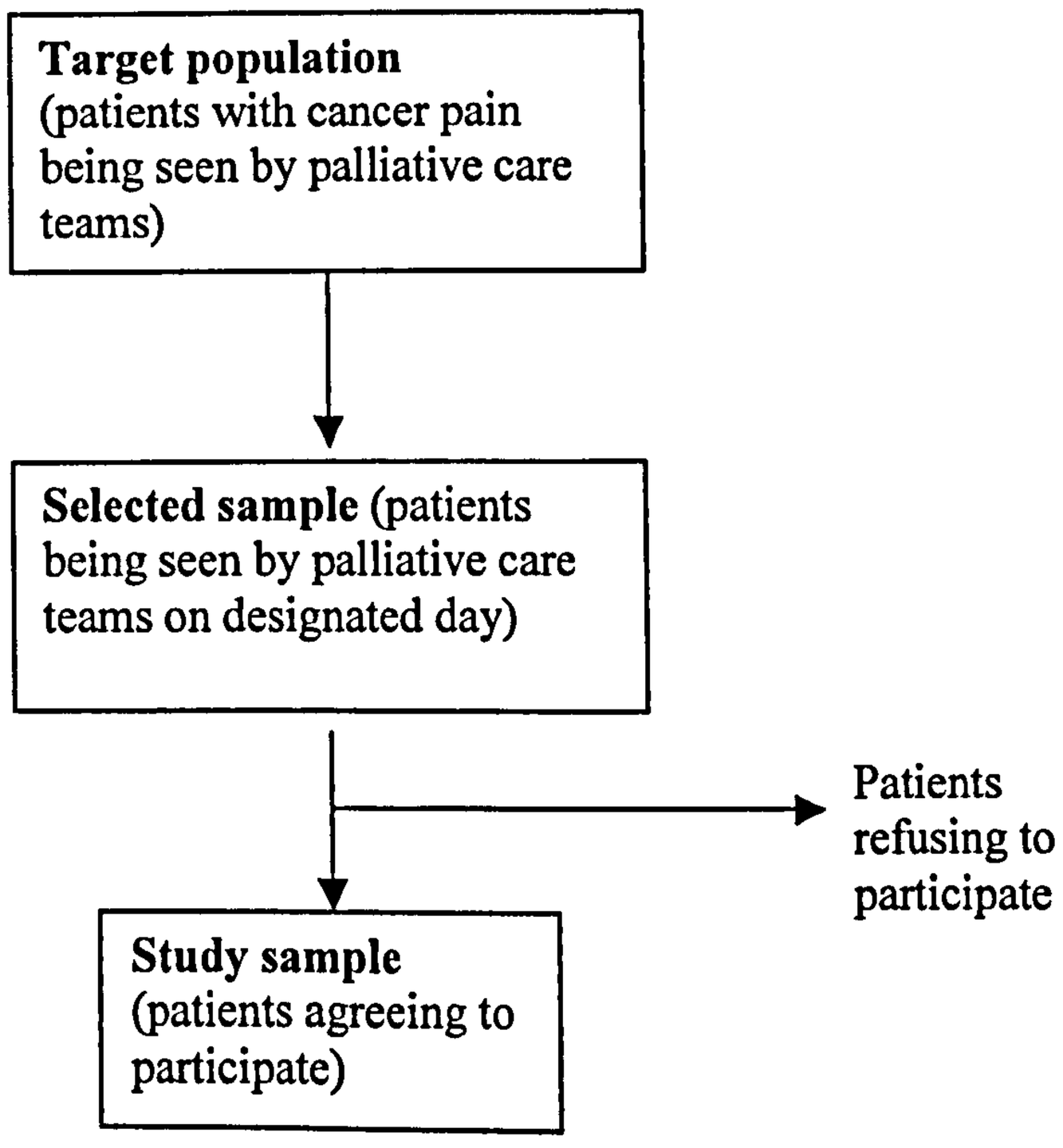
2.1.2 Cross-sectional design

A cross-sectional study is an observational study designed to measure the health experience of a population at a snapshot in time.[138] As the unit of such a study is the individual, it is possible to examine individual characteristics that might be associated

with the condition under investigation. In this study the aim was to investigate factors associated with poor pain control.

Cross-sectional studies generally involve a geographically defined representative sample of the target population of interest (the target population is that to which the results will be extrapolated) (Figure 2). The sampling frame is that group of patients from whom the study patients will be drawn. The selected sample consists of those patients randomly selected to be approached about the study and the study sample consists of those patients who agree to participate. The response rate is measured by the proportion of the selected sample that actually participate. A high response rate is important to be confident that the results are not influenced by selection bias (selection bias occurs if the characteristics of those who participate in the study differ from those who don't).

Figure 2: Recruitment to cross-sectional studies



This study was designed to measure cancer pain control by a single group of professionals: palliative care professionals. There were two reasons for this. Firstly, I assumed that palliative care professionals have expertise in pain management and are familiar with the WHO ladder, so it was likely that the ladder would be applied appropriately for each patient with pain. Secondly, I assumed that because palliative care professionals are familiar with the use of Step III opioids, then the reluctance of professionals to commence morphine or an alternative opioid would not have an influence on the results obtained. I hoped that using a cross-sectional method would mean that results could be obtained efficiently, providing an estimate of pain prevalence for this group of patients and also provide an estimate of the percentage of patients for whom the WHO ladder was controlling their pain.

2.1.3 Sample size calculation

The sample prevalence obtained from a cross-sectional study could differ from the true population prevalence because (assuming no selection bias) it is dependent on sampling variation (i.e. which of the potentially eligible participants are included in the sample).[140] However, the precision of the prevalence estimate can be measured by calculating confidence intervals. The narrower the confidence intervals, the more likely it is that the estimate of uncontrolled pain prevalence obtained would approximate to the true population prevalence.

The formula for calculating the standard error of a proportion (which allows the confidence intervals to be calculated) is:

$$\sqrt{[p\,(1-p)/n]}$$

where n = study population number. Hence the width of the confidence intervals depends on the sample size.[140]

If the approximate prevalence estimate is known, then it is possible to calculate the required sample size (the number of patients needed to be included in the study) in order to obtain narrow confidence intervals. If the true figure of patients whose pain is controlled using the WHO ladder is 80%, then it is possible to calculate the number of patients with pain required to be included in the study, in order to obtain this figure within confidence limits of between 75-85%. I performed this sample size calculation using Stata.[141] 250 completed questionnaires from patients with cancer pain would have 80% power to obtain a result within these confidence intervals, at a level of statistical significance of 5%. In order to obtain this number of questionnaires, I estimated that with an approximate figure of 5% missing data, 20% failure to complete the questionnaire by the health professional, a suggested 20% refusal rate, and an overall pain prevalence of 64% in palliative care populations[10] I needed to approach 250*1.05*1.2*1.2*1.35 =510 subjects to achieve this sample size, but only required 425 completed questionnaires from all patients, which should mean that 250 questionnaires would be from patients with pain.

2.1.4 Study documentation

Documents prepared for the study included an information sheet written for the patients, explaining the reason for the study and why they had been asked to participate (Appendix 3). The purpose of the information sheet is to ensure that patients have access to sufficient information to allow them to give their valid informed consent to participate in a research study. In preparing the information sheet I followed the

guidance for researchers that is available on the Central Office for Research Ethics Committees website (www.corec.org.uk). A consent form was also designed according to the COREC website template, (Appendix 4) which suggests that each patient not only signs the consent form, but that prior to this they are reminded of what they are giving their consent for and, if possible, write their initials in boxes placed alongside this information to show that they have understood it. The other documents developed were the patient and professional questionnaires designed to capture the information required to answer the survey questions.

2.1.4.1 Patient questionnaire: Pain scale

One of the issues in designing the patient questionnaire was deciding which pain scale to use. The original scale used to measure or rate the efficacy of pain control in the WHO ladder validation series was a patient self-rated pain relief tool,[47] which eventually had to be abandoned because of the difficulties experienced in its use. Several different pain scales have been validated for use in pain studies. They are either uni-dimensional i.e. measuring current pain severity only or multi-dimensional (either measuring more than one dimension of pain such as pain interference with function or measuring more than one pain severity e.g. pain now, pain worse, pain least and pain average). The commonly used single-dimension scales are the Visual Analogue Scale[142] which is a 100mm line anchored by "no pain" at the left side and "worst pain" on the right side. The patient is asked to place a mark on the line at a place that corresponds to their level of pain. The distance from the left anchor point to the mark represents the patient's pain score. The VAS has been shown to be valid and reliable and to be sensitive to change and so is often used in clinical trials. However, its ease of administration reduces with age and increases with experience of the administering

staff both of which were factors for this survey.[143] It was likely that patients from all age groups would be participating and the staff recruiting them would not necessarily have experience in the use of the VAS for research purposes. A further factor influencing the choice of scale is that the VAS requires a measurement to be taken by the investigator, making it more time-consuming and perhaps more open to error when entering the data into a database. A second, commonly used single dimension scale is the Numerical Rating Scale.[144] This consists of the numbers 0 – 10 in a line, anchored by "No pain" at 0 and "Worst imaginable pain" at 10. Patients are asked to circle or mark the number that best describes their pain. Generally, the VAS and NRS can be considered equal in terms of validity and reliability and the choice of scale is usually determined by practical factors.[144] A report from the Expert Working Group of the European Association for Palliative Care suggested that the numerical rating scale was the easiest scale to apply and was associated with better compliance.[143]

The decision to use a worst pain score ≥ 5 as a score representing uncontrolled pain was for two reasons. One of the most commonly used multi-dimension scales in research studies is the Brief Pain Inventory (BPI) developed initially as the Wisconsin Brief Pain Questionnaire and subsequently modified to the BPI.[145] This scale includes quantification of the extent to which pain interferes with general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life with each factor being measured on separate numerical rating scales. The authors have done methodological work with the BPI and have been able to show that worst pain levels correlate best with pain interference[5 145] and that using a worst pain score of ≥ 5 as a cut-off point allows investigators to determine the proportion of patients in whom pain is significantly more likely to interfere with function or is "uncontrolled".[5] The second

reason was that the two large pain prevalence studies conducted in France[64] and the United States[62] and the Scottish pain survey[65] all used a worst pain score of ≥ 5 to signify poorly controlled pain.

Thus, for the purposes of this study, four separate numerical rating scales, asking about pain worst, least, on average and now were included in the questionnaire, to improve ease of administration, compliance, ease of handling the data and to allow comparisons with other cancer pain surveys.

2.1.4.2 Patient questionnaire: design

I attempted to keep the patient questionnaire as simple as possible, by limiting it to one side of A4 paper and asking clear questions (Appendix 5). The first three questions asked for demographic data (age, sex and postcode). Patients not wishing to participate in the survey were asked if it would be possible for the professional to collect age and sex data so that we could determine if this group varied in any important way from the study sample (i.e. an assessment of selection bias). The next question asked whether or not the patient experienced pain, or required painkillers. Patients not experiencing pain or using painkillers did not answer any further questions and were thanked for their participation. Those who did experience pain were asked to rate their pain at its current (pain now), least, worst and average levels over the past week. They were also asked about the presence and number of episodes of breakthrough pain. The final question asked "Overall is your pain controlled?" The reason for this final question was to compare the responses to this question with the scores from the validated "worst pain" numerical rating scale, but also to see if it is possible to develop a simple pain question that might be used in the consultation to differentiate between patients with well-

controlled and poorly controlled pain. I deliberately did not ask about satisfaction with pain control as patient satisfaction with pain relief has been shown to be influenced by measures other than pain scores.[146]

2.1.4.3 Piloting the questionnaire

Once ethical approval was obtained, the original questionnaire was piloted at my own site (United Bristol Healthcare Trust) in order to ensure it was easy to understand, quick to complete and made sense to patients. Ten patients admitted to wards and seen in out-patients were asked to complete the questionnaire. All 10 patients found it straightforward and completed it in less than five minutes. A patient with impaired vision also managed to complete the questions with the assistance of a research nurse. However, it was noted that several patients scored their worst pain at 9 or greater, yet answered yes to the final question "overall is your pain controlled?" When asked about this, they all replied that although they experienced severe episodes of pain, they considered their pain to be controlled if the medication available for this pain ("as required" or breakthrough medication) worked. This piloting led to the addition of another two questions, asking about availability and effectiveness of breakthrough medication. The final questionnaire was piloted on a further five patients who again found it easy to complete. No further changes were made.

2.1.4.4 Professional questionnaire

The professional questionnaire was designed to capture information about the pharmacological management of the patient's pain along with information about the patient's cancer, performance status and the nature of the pain (Appendix 6). Questions were asked about other measures used to control pain including anti-cancer treatments

(radiotherapy and chemotherapy) and whether or not a nerve block had been tried. When opioids were used, information was obtained about the dose, route (including epidural and intra-thecal) and how many different opioids had been used (i.e. the number of opioid switches). A final question asked how long the patient had been known to the palliative care team. Each question was answered by ticking a box, apart from when including drug doses, which were to be written in full. Initially the professional questionnaire was designed to be on two sides of A4 paper only, for brevity. However, after amendments suggested by experienced clinical researchers, it was extended to a 4-sided booklet to make it easier to read and to include the instructions for professionals on the front page, so that these would be immediately accessible for all involved in recruiting patients.

2.1.5 Measuring socioeconomic deprivation

Socioeconomic deprivation was measured by matching the postcode for each patient to a Super Output Area (SOA) for which the Index of Multiple Deprivation (IMD 2004) score and quintile was known The IMD 2004 is a measure of multiple deprivations and is made up of seven domain indices: income, employment, health deprivation and disability, education, skills and training, barriers to housing and services, crime, and living environment.

2.1.6 Data management

Each individual question was given a number (1, 2 etc.) and if necessary sub-questions were labelled (e.g. 1a, 1b etc.) Each individual question also had codes assigned to responses (e.g. Yes = 1, No = 2). The results were entered into an Access database which had been designed for the study and was programmed to prevent errors by

setting limits and validation rules for each data point entered. In order to ensure maximum accuracy, all data entries were checked by a second person.

2.1.7 Recruiting palliative care teams

In order to achieve a sample size of 425 completed questionnaires (to obtain 250 questionnaires from patients with pain), it was necessary to conduct a multi-centre study because it would not have been possible to recruit this number in a convenient time frame from a single centre. I invited all of the palliative care teams in the South West of England to participate in the survey because this is a group of professionals with whom the Department of Palliative Medicine already had some established educational links. Keeping the participating teams to a geographically defined area would also mean that the survey would be easier to facilitate as a single researcher. The names of both the lead nurse and consultant for each team were taken from the Hospice and Palliative Care Directory United Kingdom and Ireland 2004 and entered into an access database along with their contact details. In December 2004, the database was used to send a mail-merge letter to each nurse and lead consultant explaining the reasons for the survey and inviting them to participate (Appendix 7). A copy of the provisional patient information sheet and consent form were included, as well as a copy of both the patient and professional questionnaires. Comments were invited on all of these documents, as I felt that it was important to hear the views of the collaborators at this stage of the study. Clarification about the potential participants was required for one team, and amendments to both the patient and professional questionnaires were made after feedback from another.

2.1.8 Research governance

In 2001, as a result of high profile research misconduct which had caused public distress, the Department of Health released a document called the Research Governance Framework for Health and Social Care, setting the standards for future research in health and social care.[147] Version 2 was released in 2005, defining the broad principles of good research governance that are key to ensuring that health and social care research is conducted to high scientific and ethical standards. The standards were to be understood by all those either engaged in research or hosting and managing research. They set out the processes to be followed for approval to be obtained for a research project and the care required to both protect patients and ensure confidentiality during health and social care research. This document, along with The Medicines for Human Use (Clinical Trials) Regulations 2004 that came into place in April 2004 has put in place standard processes which must be adhered to when conducting clinical research in the United Kingdom.

2.1.8.1 Sponsorship arrangements

Since April 2004 it has been a requirement that all research projects must have a sponsor. This role does not simply mean financial support, although it can incorporate this. The sponsor takes on the overall responsibility for ensuring the adequacy of the design and management of the study, including assessing the quality of the research and ensuring appropriate arrangements for conduct and monitoring of the research. Examples of organisations that can take on the role of sponsor include research councils and charities, universities and NHS trusts. Because this study was being conducted as part of a postgraduate degree under supervision provided by the University of Bristol, I applied to the University to request sponsorship for the study. This was facilitated by

the survey having already been peer-reviewed as a requirement of registering for a postgraduate degree. This was granted provisionally in January 2005, subject to satisfactory ethical and NHS trust research and development (R&D) approvals.

2.1.8.2 Ethical approvals

All research being conducted with NHS patients must have been considered by a research ethics committee and ethical approval granted. Since this was a multi-centre study, an application for ethical approval was made in March 2005 to the South West Multi-centre Research Ethics Committee (MREC), using the on-line Central Office for Research Ethics Committees (COREC) application form version 4.0 (Appendix 8). The initial MREC approval process resulted in additional documents (an invitation letter {Appendix 9} and consent form for each professional recruiting patients to the study {Appendix 10}) and alterations to the consent form. The committee also requested that a letter be sent to general practitioners of those patients recruited from either day-care or domiciliary settings, to inform them of the study. Approval for the study was given in May 2005 (Appendix 11).

Each participating palliative care team involved required a named local investigator, so local ethical approvals were required from each Local Research Ethics Committee (LREC). This approval process required the completion of 25 separate Section Cs of the on-line COREC form and the final Site Specific Assessment was completed in September 2005, four months after approval from the MREC.

Following this process, the data protection officer at Gloucestershire Hospitals NHS Foundation Trust was concerned that the collection of postcode data meant that the

questionnaires were not completely anonymous and that patients should be informed about this. These concerns were discussed with the administrator of the South West MREC who agreed that this had been overlooked during the original ethical review. The patient information sheet was therefore amended and a Notice of Substantial Amendment sent to the South West MREC to seek their approval for this amendment (Appendix 12).

2.1.8.3 NHS R&D Approvals

The Research Governance Framework for Health and Social Care meant that as well as obtaining ethical approval for each site it was also necessary to obtain local hospital trust R&D approval for those teams who would be recruiting from NHS trusts. The framework was meant to standardise the process of obtaining R&D approvals, and completion of the on-line COREC form facilitated completion of a Standard NHS R&D Application Form by cross-population of information to the R&D website. Not all of the trusts in the survey accepted the NHS Standard R&D form, so 15 different applications were made to NHS Trust R&D departments. The final R&D approval was obtained approximately seven months from the time of the original MREC application.

2.1.8.4 Site visits

In the month before each site was due to conduct the study, a visit was made to each recruiting centre, in order to meet the principal investigator and to speak to as many as possible of the professionals who would be recruiting patients to the survey. The Medicines for Human Use (Clinical Trials) Regulations 2004 state that it is good clinical practice for each participating site in a study to have an Investigator Site File (ISF) within which the essential information and documentation for the study can be

found. 30 site files were compiled, containing study contact numbers (Appendix 13), a copy of the instructions for principal investigators (Appendix 14), a subject recruitment record (Appendix 15), a staff signature log and delegation of tasks form (Appendix 16), the study protocol and copies of ethics and R&D applications and approvals. A copy of the trial sponsorship and insurance arrangements (Appendix 17), copies of all the information sheets, letters to GPs (Appendix 18) and questionnaires were also included along with a section to store copies of the signed professional and patient consent forms. The ISFs were given to the local principal investigator along with the actual study documents which had been grouped into "patient packs". Each "patient pack" contained all the necessary documents required to recruit a single patient to the study. This included the patient information sheet and consent form, a patient and professional questionnaire with matching study ID numbers (unique to each patient), an A5 size envelope for the patient questionnaire and a larger A4 envelope in which the professional questionnaire, the consent form and the smaller envelope were to be placed. Both the envelopes were also marked with the same study ID number. It was hoped that this would mean that the recruitment of patients in their own homes by the community palliative care nurses would be simple, requiring only one pack to be taken into the house.

The instructions were explained to all members of the teams present at the site visits. Any remaining questions were dealt with and arrangements made for return of the questionnaires. For centres recruiting large numbers of patients I decided to use a courier collection service. For those centres recruiting less than ten patients, the Royal Mail™ registered delivery service was used.

2.1.9 Study process

Each team designated one day during September that was convenient for them to conduct the study. All patients seen on that day were to be asked if they wished to read a patient information sheet and to consider participating in the study. If a patient declined to enter the study, the professional requested permission to collect demographic data, and if given, the patient consent form was completed appropriately. If the patient agreed to fully participate, they were asked to initial each of the boxes on the consent form and then to sign to confirm their consent. They were then given the questionnaire to complete. The instructions to the professional asked that if possible, the patient questionnaire would be completed independently of the healthcare professional who had recruited the patient to the study, in order that the patient could be honest about their pain scores. An informal carer or a volunteer in in-patient units could assist if necessary. The patient was then to place the questionnaire directly into the smaller envelope.

The professionals were advised to complete the professional questionnaire at the same time as the patient completed theirs. All patients seen on the designated study day were to be asked about participation until all the patient packs had been used, however, the protocol stated that the professional should not approach any patient about the study if they did not consider it appropriate. It was thought likely that this would exclude patients who were actively dying or unduly distressed.

2.1.10 Statistical analyses

The percentage of patients experiencing pain due to their cancer was calculated.

2.1.10.1 Pain scores:

Using only those patients who experienced pain, the percentage of patients with a "worst pain" score of ≥ 5 was computed.

Patients with "worst" pain scores of <5 were compared with those with "worst" pain scores of ≥ 5 using t-tests for continuous variables and chi-squared tests for categorical variables.

Those reporting a numerical rating scale score of ≥ 5 for "worst" pain were compared with those answering "No" for the question "Overall is your pain controlled?" using the chi-squared statistic.

2.1.10.2 Pain management

The proportion of patients on each Step of the WHO ladder was calculated.

The adequacy of pain treatment was assessed using the Pain Management Index (Introduction: 1.5). A PMI of -3 to -1 suggests a patient is undermedicated. A PMI of 0 to 3 suggests a patient is adequately medicated.

The proportions of patients who had received oncology treatments and adjuvants for pain was control were calculated.

The proportion of patients who did not have any drug treatment for breakthrough pain was calculated.

The proportion of patients requiring an opioid switch was calculated.

2.2 Oxycodone for cancer-related pain: meta-analysis of randomised controlled trials

As stated previously, the re-launch of oxycodone in a formulation suitable for use in chronic pain has led to a great increase in its use. Whilst it was likely that the practice of opioid switching to relieve persistent side effects caused by other opioids[84] would explain some of this increase in its use, anecdotal evidence from personal experience suggest that some professionals consider oxycodone to be a superior opioid to morphine and are using it as their first-choice opioid. This seems to be because there is some evidence from randomised controlled trials of its use in cancer pain that it might have fewer adverse effects than morphine.[75 76] Some authors have also suggested it is a superior opioid.[79 81] However, the evidence base is relatively weak, with only a few published randomised controlled trials reporting data on side effects.[74-76 148] It was therefore appropriate to conduct a systematic review, with meta-analysis if possible, of the available evidence for oxycodone. If oxycodone is a better tolerated opioid than morphine then it would be worth evaluating whether it should replace morphine as the opioid of choice in guidelines such as those produced by the WHO and the EAPC. Secondly, if it is not superior, given its greater cost (**www.bnf.org**) it could be argued that it should not be considered a first line opioid in health systems where cost is a concern.

2.2.1 Reasons to conduct a systematic review

A single study frequently fails to detect, or exclude with certainty, a modest, albeit clinically relevant difference in the effects of two therapies.[149] This is because many studies often lack the power to detect such a difference, due to insufficient patients being recruited. This is particularly relevant in cancer pain, where it is difficult to recruit large numbers of patients even to multi-centre trials[150 151] and subsequently trials are underpowered or simply abandoned.[136] A meta-analytical approach, where data from patients in several trials evaluating the same drug are considered and used to obtain a weighted average of the results, offers an alternative to conducting large studies and so may offer a more practical way of answering an important question. Systematic reviews may also offer more evidence about the generalisability of the results, by investigating the extent to which differing trial or patient characteristics influence the overall treatment effect.[149]

2.2.2 Limitations of systematic reviews

The main limitations of systematic reviews are that the validity of the results is dependant on the attempts to find suitable studies eligible for inclusion in the review and on the quality of those individual studies. This is because meta-analysis consists of calculating a weighted average of included studies, so if those studies are flawed because of poor quality, or if attempts to find studies are not comprehensive enough, then the results of the reviews may be biased. However, knowledge of the potential sources of bias in a review allows investigators to conduct a review which attempts to minimize bias, or at least attempts to assess the influence that any particular bias may have had on the outcome.

2.2.3 Quality of included studies

In controlled trials, bias falls into four main categories: selection bias, performance bias, detection bias and attrition bias.[152] Selection bias has occurred if the intervention and control groups differ at baseline in any important way and during trial conduct is prevented by two separate events; the appropriate generation of allocation sequence and concealment of allocation from the investigators enrolling patients. Empirical studies have demonstrated that both of these but particularly concealment of allocation, if not conducted properly, will exaggerate treatment effects.[152] Performance bias occurs when the intervention and control groups are handled in a different way; ideally all additional treatments and follow-up care provided should be equal in all study groups. Attrition bias occurs when there are losses-to-follow-up or protocol deviations, as it is likely that lost-to-follow-up patients differ in some way from those remaining in the study. If possible, all patients randomised should be included in the final analyses but pain studies usually rely on continuous outcome variables such as pain scores and so it is not always possible to include all patients lost-to-follow-up. In these studies, the proportion of patients excluded from the analyses from each group should be made available for the reader.

Different opinions exist about the measurement of trial quality within a systematic review. Some, such as the Pain, Palliative and Supportive Care (PAPaS) Review group of the Cochrane Collaboration, advocate the use of composite scales to measure quality, where information about several features of the trial are combined in a single score. This score can then be used to give additional weighting to each trial's contribution to the final estimate of treatment effect. Another approach, advocated by the Cochrane Statistical Methods Group suggests that each dimension of trial quality should be

considered individually. This is because composite scores tend to vary in both their composition, complexity and subsequently their overall indication about a trial's quality, and have also shown different results when used to perform sensitivity analyses for previous meta-analyses.[153] A further problem when deciding how to adjust for trial quality in a systematic review is that what is actually being considered is the quality of the reporting and not necessarily the quality of the trial conduct.[154] Relatively recent developments such as the CONSORT guidelines (www.consort-statement.org) have attempted to guide authors to give accurate reports of a trial's conduct but these guidelines were not available for studies reported before their publication. For this reason, the most appropriate approach seems to be to conduct sensitivity analyses that explore the associations between treatment effect and study characteristics using categorical data on individual components on trial quality.[153]

2.2.4 Other sources of bias in systematic reviews

The methods of retrieval of studies for inclusion in a review are important if all studies relevant to the intervention of interest are to be obtained. It is well known that only a proportion of research findings that are presented at conferences or as abstracts will eventually be published in indexed peer-reviewed journals.[155] Studies with statistically-significant results are more likely to be published than those without and in fact this may be a more important factor in obtaining publication than the quality of the trial itself.[155] It is also known that a large proportion of trials submitted to licensing authorities remain unpublished and so it is particularly important to attempt to retrieve unpublished data held by pharmaceutical companies. However, if unpublished data are obtained, decisions must then be made about their inclusion in meta-analysis, since it is often not possible to assess the quality of these data. Data from some large studies have

been presented more than once in published papers and including duplicated data will bias overall treatment effects. Most of these sources of bias can be eliminated by a comprehensive literature search including databases and citation lists of review articles and attempts to retrieve unpublished data or papers published in languages other than English with a protocol stating unbiased pre-defined inclusion/exclusion criteria.

2.2.5 Quality of systematic reviews

The overall quality of a systematic review requires assessment by the reader, if reviews are to fulfil their potential of providing clinicians with a means of keeping up with the medical literature by summarising the accumulated research. A systematic review should provide a statistical aggregate of relevant studies which have been systematically identified, appraised and synthesised according to a pre-determined explicit methodology. A conference of epidemiologists and clinicians resulted in the dissemination of the QUORUM statement, which provides a tool for the conduct and reporting of systematic reviews.[156] The methods of the QUORUM statement were followed in both the conduct and subsequent publication of this review.[157] Ideally, in order to minimise any bias, a protocol should be written at the outset and adhered to as in any other research study and advice should be taken from clinicians with knowledge of the clinical problem and from experts in research synthesis. A further source of help in research methodology is the Cochrane Collaboration, an international organisation that aims to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews and by developing methods to be used in systematic reviews.[158]

2.2.6 Review protocol

With the help of Professor Matthias Eggar and Dr. Jonathan Sterne in the Department of Social Medicine, at the University of Bristol, a protocol was written, to define "a priori" those studies which would be considered for inclusion and the methods to be used to identify studies and extract data from the study reports. We also decided to conduct the review with assistance from the Pain, Palliative and Supportive (PaPAS) Care Group of the Cochrane Collaboration to ensure that the results would be made available to a wider audience.

2.2.6.1 Identification of eligible studies

The inclusion criteria are dependant on the question being considered, which for this review was the effectiveness and tolerability of oxycodone in the treatment of cancer pain. I therefore planned to include randomized controlled trials, comparing oxycodone with either placebo or an active analgesic drug, in patients with cancer-related pain in any treatment setting. All routes of drug administration and all formulations of oxycodone were to be considered. Only those studies reporting patient-assessed outcome measures were to be included. Studies comparing combination oxycodone preparations (e.g. fixed-dose oxycodone combined with paracetamol) were excluded.

2.2.6.2 Search Strategy

Along with Sylvia Bickley, the Trials Search Co-ordinator for the PaPAS Group, I designed a detailed search strategy to include all possible names for oxycodone in combination with appropriate MeSH headings for pain and cancer (Appendix 19): I searched the following electronic databases Cochrane Pain, Palliative and Supportive Care Register 2002; Cochrane Controlled Trials Register 2002: Cochrane Library

current issue; MEDLINE (1966 – 5/2002); EMBASE (1980 – 5/2002); CancerLit (1960 – 5/2002); and CINAHL (1982 – 5/2002). In order to minimise the effects of publication bias and to retrieve any unpublished data, I also searched Dissertation Abstracts (2002) and SIGLE (2002). I hand-searched reference lists of any retrieved articles and other relevant literature such as pain or opioid reviews. I wrote to the manufacturers of oxycodone preparations (Napp Pharmaceuticals U.K. and Purdue Pharma U.S.A), to known oxycodone investigators and to experts in the field to request any unpublished data on oxycodone in cancer pain. I also made a request to subscribers of the journals *Palliative Medicine*, *Journal of Pain and Symptom Management* and *Pain* for data from unpublished trials or information about other trials I had not identified. I distributed flyers at a major opioid conference and a Palliative Medicine conference making requests for any information regarding unpublished data on oxycodone. The search strategy was repeated in April 2005.

2.2.6.3 Selection of studies suitable for inclusion

In order to avoid error in assessment of whether studies met the inclusion criteria, two separate researchers (myself and Dr. Andrew Davies) read the study abstracts obtained after conducting the original searches, and then completed a form stating whether or not the full study report should be retrieved. If it was not considered necessary to retrieve the full article, reasons for exclusion were noted on the form. A record of excluded studies was kept so that they could be entered into RevMan (systematic review software provided by the Cochrane Collaboration) and so could be made available to interested readers.

2.2.6.4 Data Extraction

The full text versions of potentially eligible articles were then obtained and independently assessed for inclusion by myself and Dr. Davies. We initially screened for duplicate publications by reviewing study name, authors, location, study population, dates, and study design, and then by confirming with the study authors that each of the included reports did indeed represent a separate study. Other reasons for excluding a trial were recorded. For eligible trials, we independently extracted data from the article using a specifically designed data extraction form. This form recorded the following: publication details, patient population details, nature of pain if described, interventions, outcome measures used, analgesic (efficacy) results and adverse effects (tolerability) data. We also extracted data on reported methods of generation of the allocation sequence, concealment of allocation and the blinding of patients, clinicians and outcome assessors and whether or not analysis had been by intention to treat in each trial, in an attempt to assess the quality of the studies to be included in the review.

2.2.7 Systematic review and meta-analysis

Meta-analysis involves a 2-stage process whereby appropriate summary statistics are calculated for each included study and then these summary statistics are combined to provide a weighted average of the results, described as the pooled estimate of treatment effect. Continuous data are usually combined as a difference in means or as a standardized difference in means if a mixture of measurement scales has been used in the included studies. To obtain a standardized mean difference, each individual study mean difference is divided by its standard deviation (SD) to obtain a set of results standardized to a uniform scale (the size of treatment effect in each trial relative to the variability observed in that trial).[159] These data may then be combined using a fixed

effects model where the weight is calculated for each study according to the quantity of information it contains. If hetereogeneity between the individual study findings is demonstrated by statistical methods, then an estimate of the between study variation is also incorporated into the calculation of the common effect, using random effects meta-analysis. Generally the weights in a random effects model will be smaller and more similar to each other than the weights in a fixed effects analysis and the estimated treatment effect more likely to be conservative, with wider confidence intervals. The method to be used for meta-analysis therefore depends on the data type, the choice of summary statistic and the observed heterogeneity between the individual studies. The weighting of each study is related to the individual study variance, which is closely related to the sample size and it is for this reason that large studies often carry more weight. Meta-analysis is not therefore simply a combination of the data from all trials as if they represented a single large trial.

For continuous outcomes, meta-analysis requires the number of participants and the mean response with its standard deviation for both intervention and control groups, in order that the summary statistics can be calculated. If appropriate, once the main meta-analysis has been conducted, further sensitivity analyses can be undertaken to ascertain the robustness of the data. An example of such a sensitivity analysis is when the meta-analysis is repeated after exclusion of poor quality trials. The more consistent the obtained summary statistic is with repeated analyses, the greater justification exists for expressing the effect of treatment in a single summary number.

2.2.7.1 Particular considerations for this meta-analysis: incorporation of crossover trials into a meta-analysis

Most meta-analyses are of randomised controlled trials where patients are randomised to two different parallel treatment groups. However, a particular feature of the pharmacological treatment of chronic pain is that it fulfils the necessary criteria for crossover designs i.e. it is a chronic condition which doesn't alter greatly during a short study duration, it is subject to temporary relief during treatment and will recur after the withdrawal of treatment.[160] Crossover trials also require fewer patients to produce the same precision as a parallel group trial because each subject acts as their own control and within-subject variation is usually less than between-subject variation. This is frequently exploited when examining chronic pain caused by cancer because as stated previously, it is often difficult to recruit large numbers of patients to these trials. Particular issues when considering inclusion of crossover trials within systematic reviews and meta-analyses are around the quality of the reporting of the data, how much of the data to include and whether or not the results of crossover trials can be combined with results from parallel group studies. Although crossover trials are usually powered by sample size calculations which take into consideration their increased statistical power, their results are not always reported as within-subject treatment differences. Instead, the mean and its standard deviation for assessments after treatment and the mean and its standard deviation for assessments after placebo are often reported, as if the data were obtained from a parallel group trial. However, these data are unsuitable for inclusion in meta-analyses because they do not take account of the fact that the patients in a cross-over trial receive both treatments and hence the groups are not independent of one another; a requirement for meta-analysis.[161] Also, the effects of simply pooling the results from both periods may exaggerate the benefits of the more

successful treatment.[161] Authors of other systematic reviews have chosen to use the data from the first period only and use these data as if they had been obtained from a parallel group trial. However, these data are not always available, and if in fact they are, they may represent biased data, the authors having chosen to display these data because of a favourable treatment effect. In addition, the data obtained from the first period only may be underpowered to detect or exclude important differences. Ideally, the results from the paired analyses should be included in meta-analysis. This requires an estimate of the within-person comparison of treatments and its standard deviation (or standard error or confidence interval to allow calculation of the standard deviation). If the within-person correlation of scores is also known, then the study variance can be calculated and used to conduct the meta-analyses.

2.2.8 Data retrieval

The original trial reports did not contain sufficient data to allow meta-analysis, mainly because four of the included studies were crossover studies, where the authors provided mean pain scores for patients whilst on oxycodone in comparison with mean pain scores for patients whilst on control drug i.e. the results were reported as if from a parallel group trial. The parallel group trial also did not report mean differences in pain scores (e.g. the mean individual difference in pain scores comparing Day 1 with the last study day) but instead reported group mean pain scores. This problem has been encountered in other systematic reviews of opioids in cancer pain and the authors conducting these reviews have chosen to report the findings in a qualitative overview of results.[82 162] A recent paper by Elbourne and colleagues[161] suggested that this was usual practice in Cochrane reviews, with authors either choosing to omit the results from crossover trials or using other methods to include their data. However, a recently

conducted systematic review of opioids in breathlessness[163] had encountered similar difficulties with the reporting of trial outcomes and those involved also reported the methods used to counter these difficulties.[161] In order to try to replicate these methods, we contacted Napp Pharmaceuticals (the sponsor of the included studies) and the individual study authors to request further pain data from the trials. An initial request for individual patient data was granted by one of the authors,[75] but refused by Napp Pharmaceuticals. A second request was then made for summary statistics (the mean within-patient difference comparing each patients' pain scores on the last day of the control phase with the last day of the oxycodone phase and its standard deviation) in order that meta-analysis of these data could then be undertaken. This second request was granted six months later following several discussions with the owners of Purdue Pharma based in the United States, the parent company of Napp Pharmaceuticals in the U.K. After the initial analyses of the efficacy data, a request was made to Purdue Pharma via Napp Pharmaceuticals for individual patient data on the presence or absence of side effects recorded in the studies. These data were also eventually granted after a further six months.

2.2.9 Consistency of results (testing for heterogeneity)

The value of the overall estimate of treatment effect obtained by a meta-analysis is sometimes limited when the included studies have shown differing results. For this reason, attempts are usually made to establish the consistency of the results obtained from each study, particularly as this can then lead to an assessment of the generalisability of the overall result. A test for heterogeneity seeks to establish whether the results are genuinely different between studies (heterogenous) or whether they are actually the same (homogenous) but the differing results obtained have arisen by

chance due to sampling variation. The results of tests for heterogeneity are also used to determine which methods should be used to combine the study results (i.e. to use either the fixed or random effects methods as described above). Tests for heterogeneity such as Cochran's Q test are limited when dealing with a meta-analysis including only a small number of studies, whereas the I^2 statistic is more sensitive because it provides a quantification of the inconsistency (and so can be used to determine the effect to which the inconsistency affects the conclusions of the meta-analysis).[164] The I^2 statistic lies between 0 and 100% and represents the percentage of total variation across the studies that is due to heterogeneity rather than due to chance. It can also be quantified, with 25%, 50% and 75% representing low, moderate and high heterogeneity respectively.[164]

2.2.10 Investigating heterogeneity

Meta-analysis is a synthesis of data from several different clinical trials which often have encompassed a variety of different regimes, participants and outcomes. This clinical heterogeneity may mean that the results are incompatible because of observed statistical heterogeneity. However, it is not sufficient to simply assess the amount of heterogeneity. An exploration of the source of the heterogeneity using meta-regression methods allows an investigation into how the different trial or patient characteristics have influenced the treatment effects.[159] A certain degree of caution is required in the results obtained from meta-regression analyses since they are, in a way, comparable to the results of sub-group analyses of controlled trials. However, more confidence can be placed in results from meta-regression analyses if either indirect evidence or biological considerations support their findings.

2.2.11 Statistical methods used

Since the statistical combination of the data from cross-over and parallel group trials is complex, the meta-analysis was conducted with help from epidemiologists at the Department of Social Medicine at the University of Bristol (Dr Richard Martin and Professor Jonathan Sterne). We analysed the mean within-person difference in pain scores recorded on the first study day and those recorded on the final day on each study drug (to ensure steady state had been reached). Different assessment scales were used to record pain scores in the trials so treatment effects were expressed as standardised weighted mean differences.

To validly combine the results from the cross-over trials with the parallel group trial, the following parameters were estimated. For the parallel group trial, the standardised weighted mean difference was calculated using Glass's estimator[159] (p.291) and the standard error calculated according to equation 9 of Curtin and colleagues.[165] For cross-over studies, standardised weighted mean differences were estimated according to equation 11 of Curtin and colleagues,[165] by dividing the treatment effect by the between- plus within-subject standard deviation of the cross-over differences. To estimate the standard deviation of the cross-over differences a common between-period intra-class correlation coefficient of 0.2 was estimated using individual level data available only for the Heiskanen trial.[75] Estimates of the variance of the cross-over effect sizes were then derived by equation 14 of Curtin and colleagues.[165] Since the trials used different control groups (morphine or hydromorphone), and there was evidence of between-trial heterogeneity, they were pooled using random effects meta-analysis.[159] We obtained data on the presence or absence of 16 common opioid-related side effects from the authors of each crossover trial and calculated the marginal odds

ratio estimate described by Becker and Balatgas[160] to obtain odds ratios and their standard errors for the crossover trials. For each side effect, these odds ratios were combined with the corresponding odds ratio derived from the published report of the parallel group trial.

2.2.11.1 Statistical Software

Analyses were conducted using Stata version 8 (meta-analysis of pain outcomes) and RevMan version 4.2.7 (meta-analysis of side effects). Dr Martin and Professor Sterne conducted the meta-analysis of pain outcomes. I conducted the meta-analysis of side effects, under the supervision of Drs. Martin and Sterne.

2.3 The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Some have considered it impossible to conduct a randomised controlled trial of the WHO ladder[166] despite Jadad and Browman[51] considering this to be exactly the study required to assess its efficacy. It is likely that a trial of two different approaches (or ladders) to manage pain would need a different design from a trial comparing two analgesic drugs, but it seems important to attempt such a study in order to answer questions about the continuing efficacy of the ladder.

2.3.1 Napp Pharmaceuticals Pilot

Napp Pharmaceuticals began a pilot study for a trial of a two-step versus a three-step approach in September 2003 as a multi-national, multi-centre study, recruiting in both Spain and the United Kingdom. The Department of Palliative Medicine at the University of Bristol was one of the recruiting centres for this study and had been closely involved with the study design and protocol development. Several months into the trial, with 19 patients already recruited, Napp Pharmaceuticals withdrew their sponsorship, citing poor accrual rates.

The Department of Palliative Medicine decided to apply for funds to continue the pilot study in three centres, Bristol, Nottingham and Edinburgh and for it to become the focus of this dissertation. This decision was coincident with new clinical trials regulations, the Medicines for Human Use (Clinical Trials) Regulations 2004, the aim

of which was to achieve improved and standardised conduct in clinical trials throughout the European Union. The pilot study protocol required alterations in order to comply with these new regulations, giving us the opportunity to improve its design. The most significant amendment to the protocol was the inclusion of a nested qualitative study aiming to explore the views or concerns of patients when being offered Step III opioids for the first time, described in Methods 2.4. Other modifications to the protocol included shortening the period of data collection for the primary outcome measure from eight weeks to four. This was to make use of information obtained from the original validation series,[48 56] which showed that the mean time spent at the second step of the WHO ladder was 28 days. Hence, any differences in the two approaches should be demonstrable within 28 days. Reducing the data collection period for the primary outcome measure would also minimise attrition, often a significant problem in studies in cancer pain. We also extended recruitment in Bristol to include local general practices. The other amendments were made to comply with the pharmacovigilance requirements of the new trial regulations.

2.3.2 Change of sponsor

Napp Pharmaceuticals had withdrawn their sponsorship of the trial, so an application was made to United Bristol Healthcare Trust to take on the role of sponsor (Appendix 20). This involved obtaining an external peer review, which was conducted by Professor Henry McQuay, the Chair of the Palliative Care Clinical Studies Development Group of the National Cancer Research Institute. UBHT agreed to take on the role of study sponsor in August 2004.

2.3.3 EUDRACT Registration

The new regulations state that any clinical trials must be registered on the European Database of Randomised Controlled Trials (EUDRACT) and obtain a EUDRACT number. This number is then used for all communications with either the regulatory authority (the Medicines for Human Use Regulatory Authority or MHRA) or the research ethics committees. The EUDRACT number 2004-004235-66 was obtained in October 2004.

2.3.4 MHRA Authorisation (DDX to CTA)

The new regulations state that any organisation involved in a study of an investigational medicinal product must hold a Clinical Trials Authorisation certificate in order to do so. The CTA replaced previous authorisations called the Doctors and Dentists Exemption (DDX: MLA 162 and MLA 163). All of these are regulated and issued by the MHRA. However, all trials already in progress holding a DDX when the regulations became statutory on May 1st 2004, simply had the DDX certificate for the trial transferred over to a CTA with no costs incurred. When the 2-step study had been under Napp sponsorship, a DDX had not been considered necessary because the study drugs were being used within licence. However, in view of the impending new regulations, I applied for a DDX (MLA 162 and 163) in the knowledge that this would then be converted into a CTA. This certificate was issued in June 2004 (Appendix 21).

2.3.5 Study approvals

2.3.5.1 Ethical approval

I completed a protocol amendment form (Appendix 22), available on the COREC website (www.corec.org.uk), stating the changes made to the study (the change of sponsor, protocol changes made to comply with the new regulations, the change in recruitment process and the addition of the qualitative component of the trial). This was reviewed by the South West MREC protocol amendment committee and ethical approval was given in October 2004 (Appendix 23). It was considered unlikely that the amendments gave rise to any particular site-specific issues, so separate approvals from local research ethics committees were not required for the recruiting centres.

2.3.5.2 R&D approval from UBHT

Although the study previously had trust approval from UBHT, the change of sponsor meant that I had to re-apply for trust R&D approval. This was granted in July 2004.

2.3.5.3 R&D approvals at Nottingham and Edinburgh

Both of the trusts involved at these sites requested copies of the protocol amendment form, the CTA and the letter confirming the new sponsorship agreement before R&D approval could be given. This was issued in Nottingham in March 2005 and in Edinburgh in October 2005.

2.3.5.4 North Bristol Primary Care Trust approval

In view of the changes being made to the protocol to allow recruitment to the study to take place from general practices throughout Bristol, we applied for North Bristol Primary Care Trust R&D approval which was granted in October 2004. The two

members of the research team were issued honorary contracts to allow us to visit and recruit patients in the community.

2.3.6 Good clinical practice (GCP)

The Medicines for Human Use (Clinical Trials) Regulations 2004 outline the standards to which clinical trials must be conducted in order to protect the trial subjects. These standards and principles are generally referred to as "good clinical practice". The research nurse and I undertook locally arranged training sessions in order that we were familiar with what constitutes good clinical practice.

2.3.7 Application for research funding

I co-ordinated a bid to Cancer Research UK (CRUK) via the Clinical Trials Applications and Awards Committee for funding for the study as a co-investigator with Professor Hanks, Dr Marie Fallon in Edinburgh and Dr. Andrew Wilcock in Nottingham. This was successful and £43000 was awarded to fund statistical support and salaries.

2.3.8 Maximising recruitment

This pilot study represented a challenge to recruitment for palliative care research teams, because of the need to recruit patients who are only at Step I of the ladder (i.e. using paracetamol or a non-steroidal anti-inflammatory drug for their pain control). The majority of patients being seen by palliative care professionals will have already commenced morphine or an alternative Step III opioid.[134] This trial therefore required cooperation from oncology and primary care colleagues.

2.3.8.1 Visits to general practice teams

The research nurse and I both visited each practice prepared to recruit to the study in order to explain the aims and rationale of the study. Investigator Site Files were compiled for all practices so that each would have all the necessary study documentation as well as copies of the study approvals. During these visits, arrangements were agreed for obtaining prescriptions for medications during the study. A flow diagram of the recruitment process was agreed with each practice and a copy left in the ISF (Appendix 24). This flow diagram gave the necessary contact numbers for the research team.

2.3.8.2 Recruitment within UBHT

The research nurse and myself held regular meetings with the site-specific clinical nurse specialists, oncology outpatient and day-care nursing staff and the oncology ward doctors to remind them of the inclusion criteria for the study. We offered to see any patients with uncontrolled pain attending outpatients and irrespective of whether or not they entered the trial, advice was given on pain management. This meant that the research team was at times functioning as additional members of the hospital palliative care team, but this seemed necessary in order to gain access to an adequate number of patients, by encouraging other teams to refer to us. We screened the case-notes of patients attending the twice-weekly uro-oncology outpatient clinics and the notes of patients attending the Bristol Haematology and Oncology Centre day unit for pamidronate infusions (bisphosphonates are used in the treatment of bony metastases, which are often associated with pain) to assess eligibility for the study.

2.3.8.3 Recruitment from St. Peter's Hospice

We were also able to use our links with our palliative care colleagues at St. Peter's Hospice to increase our accrual rate, by gaining access to patients with cancer pain attending day hospice and being visited by the hospice community clinical nurse specialists.

2.3.8.4 Recruitment from other Edinburgh and Nottingham

There were significant delays in recruiting from Edinburgh, mainly due to the length of time taken to obtain trust R&D approval, which was only granted in October 2005 (over one year after the corresponding approval in Bristol). Recruitment in Nottingham was also slower than in Bristol, so the research nurse from Bristol visited to share ideas about maximising recruitment.

2.3.9 My role

Once the approvals had been obtained, and the study had commenced in the various settings I continued to act as study co-ordinator, dealing with enquiries from the recruiting teams in other sites. For the UBHT site I acted as study doctor and so was involved in the recruitment procedures and liaising with colleagues to promote the study. I provided supervision for the research nurse who was appointed to assist with recruitment and clinical management of patients within the study.

2.3.10 Protocol

The study was designed as an open, randomised, parallel group study. 30 participants were to be allocated in a ratio of 1:1 to either the experimental two-step approach or the traditional three-step approach and followed up for 12-18 weeks. All patients were to

be managed by the research team although their own primary care team could make alterations to analgesic medication if necessary.

2.3.10.1 Inclusion criteria

- Patients aged 18 or over
- Patients with a confirmed diagnosis of cancer
- Patients with pain caused by their cancer, requiring (but not yet taking) Step II medication
- Patients who are able to take oral medication
- Patients willing to complete a patient diary
- Patients willing and able to give their informed consent to take part in the study

2.3.10.2 Exclusion criteria

- Patients who had used regular Step II analgesics in the two weeks before study entry
- Patients who had used regular Step III opioid in the month before study entry.
- Patients thought to be at an increased risk of the central nervous system depressant effects of the study medication
- Patients with a history of depression or personality disorder which might lead to self-harm or admission to hospital
- Patients with a known sensitivity to oxycodone or other opioids
- Patients with a history of drug or alcohol abuse
- Patients involved in research studies involving a new clinical entity
- Patients scheduled to undergo cancer-related surgery

2.3.10.3 Randomisation

Patients were sequentially allocated to treatment according to a pre-prepared randomisation schedule which had been produced in blocks of four, with separate blocks for each centre. Treatment allocations were concealed in opaque envelopes which were opened by the study doctor once the patient had given their written informed consent for the study and the research nurse had completed the screening and study entry documentation. For patients recruited in Edinburgh and Nottingham, a member of the research team or an administrator in Bristol confirmed treatment allocation by telephone.

2.3.10.4 Study medication

Patients randomised to the experimental two-step approach initially received OxyContin™ (modified-release oxycodone) 5mg twice daily with OxyNorm™ (normal-release oxycodone) 5mg as required for breakthrough pain. These patients were also routinely prescribed laxatives to use regularly and titrate as necessary and anti-emetics to use if required.

Patients randomised to the three-step approach were given co-codamol 30/500, two tablets four times a day with normal–release morphine sulphate solution to be used for breakthrough pain. These patients were commenced on sustained-release morphine sulphate tablets if their pain progressed and at this time would be given an anti-emetic and laxatives.

In both groups, analgesic medication was increased or decreased as pain levels or side effects dictated.

2.3.10.5 Visits

Patients were telephoned at the end of the first week (by the research nurse) and seen every two weeks (by me or the research nurse), until week four, after which visits were conducted monthly. Throughout the study period, all patients were advised to contact the research team if they had problems with pain control or side effects during normal working hours. Participants in Bristol were given the contact number for the on-call U.B.H.T. Palliative Medicine physician to use out-of-hours. They were also advised that they could contact their own general practitioner if they wished.

2.3.10.6 Study documentation

Patients completed a daily pain diary asking them to rate their average pain for that day on a Box Scale 11 as below.

0	1	2	3	4	5	6	7	8	9	10

They were also asked to record the number of doses of escape or breakthrough medication they had used and whether or not they had had any contact with a healthcare professional that day.

At each study assessment visit they were asked to complete a Brief Pain Inventory pain assessment tool (Appendix 25) and information was obtained about side effects or other adverse events.

2.3.10.7 Outcome measures

The primary outcome measure was the percentage of time spent in the first four weeks of the study period with a BS-11 pain score of four or less (this is considered to

represent mild pain).[63] We also planned to examine the probability of patients in both approaches having controlled pain (≤ 4) on any given day using logistic regression. Secondary outcome measures included mean BS-11 pain scores, the time taken to reach stable pain control (defined as four or more days with a score of 4 or less), mean BPI pain intensity (worst, least, average and now) and pain interference scores recorded at each assessment visit. The number of adverse events in both groups was examined as well as adherence to medication and use of breakthrough medication in both groups.

2.3.10.8 Statistical Methods

The data for the primary and secondary outcome measures were examined using appropriate multivariable regression models (that is, linear or logistic for continuous and binary outcomes respectively). Models also included stratification variables and baseline pain score as covariates. The effects of other variables such as funder and weighting for the number of pain days' data provided per patient were investigated in the secondary analyses and reported as appropriate. For repeated measures data (individual patients may have provided up to 28 days of pain data), appropriate random effects (linear or logistic) regression models were used to take account of the hierarchical nature of the data. The time taken to achieve stable pain control was analysed as survival data using Cox's regression analysis.

2.3.10.9 Imputations for missing data

If an individual failed to provide 28 days of pain data, then imputations were made according to whether or not they were alive at censoring for the primary analysis only. If they were alive, it was assumed that they had a pain score of > 4. If dead, their data

remained missing. If only one value was missing in between two available data points, then the average of those two points was calculated and that value imputed.

2.3.10.10 Safety

Adverse events were recorded, graded and assigned causality using knowledge about expected or likely side effects caused by opioids. All serious adverse events were reported to the study sponsor.

2.3.10.11 Monitoring

The study sponsor, UBHT Research and Effectiveness Department was responsible for the monitoring of the study at UBHT.

2.4 A qualitative study to explore the views of patients considering morphine for relief of pain caused by cancer

Patients have concerns when commencing opioids and in particular morphine. These concerns are likely to impact on their decisions when considering options for pain management. The two-step pilot study, discussed in the previous chapter, offered an opportunity to engage with patients with cancer pain when a Step III opioid was first offered for pain control, in order to explore these concerns.

2.4.1 A nested qualitative study

As stated previously (Introduction: 1.5), most research into patient "barriers" to cancer pain control, including fears about opioids, has employed quantitative methods to quantify or score the extent to which individuals are affected.[110 115 116] These studies have failed to show a clear relationship between barrier scores and pain scores, so it is possible we have not yet fully understood these fears, how they vary in different circumstances or how they influence pain control.

Other authors have used qualitative methods to examine in greater depth patients' views on different classes of drugs. Benson and Britten[167] explored patients' views about anti-hypertensive drugs and their reasons for adhering to drug regimens in spite of their reservations about these drugs. Grime[168] used semi-structured interviews to explore the attitudes of patients to anti-depressant drugs in primary care settings and how behaviour was influenced by actual experience of taking anti-depressants.

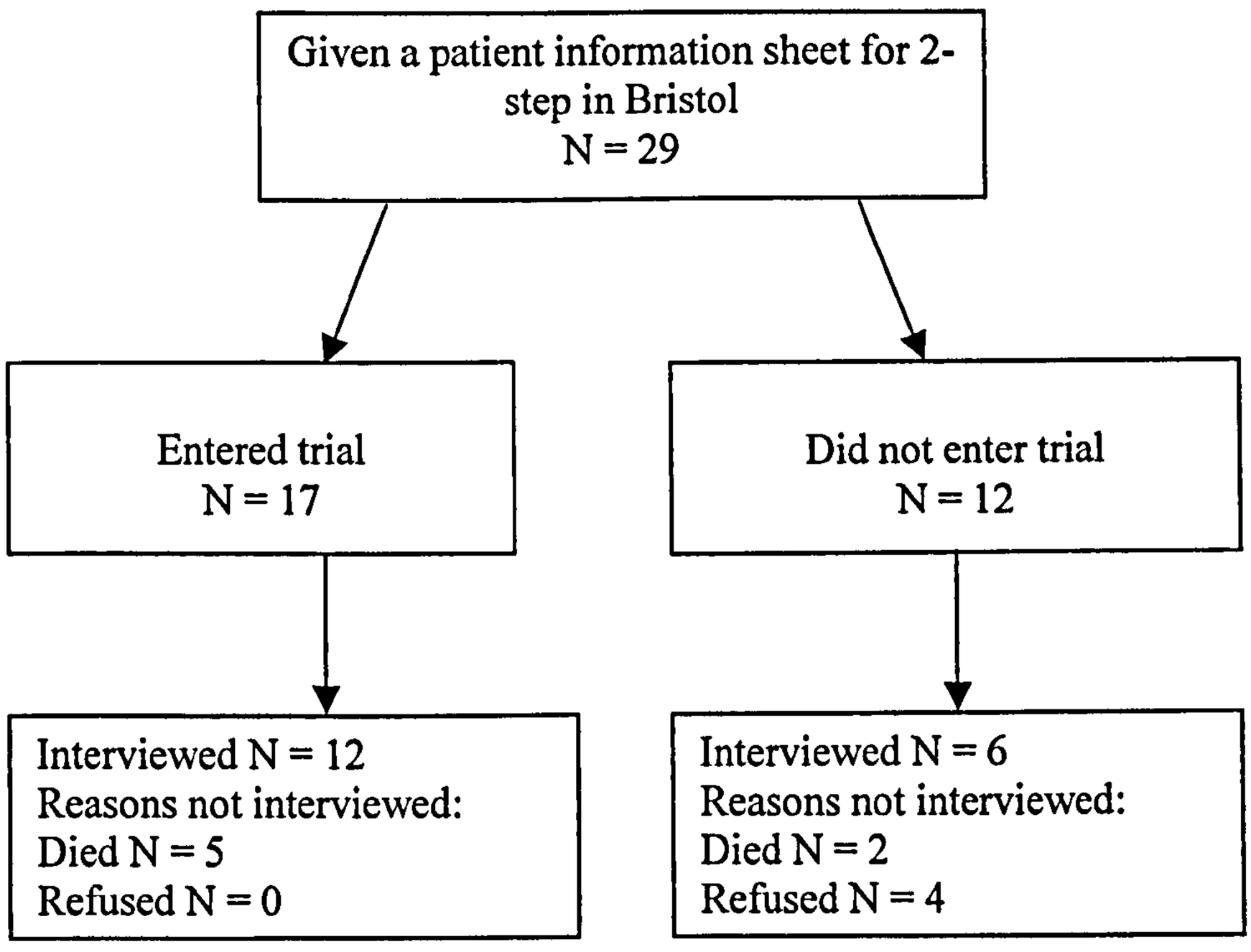
Qualitative research has been described as "research that focuses on the experience and meanings of individuals or groups in order to analyse how and why people form associations with other people, with things and with their immediate environments".[169] Clark,[170] in his paper describing what qualitative research can contribute to palliative care, states "qualitative research has the power to disrupt existing assumptions and to challenge what passes for knowledge". Using a method that did not make any assumptions, but instead used the experience of the individuals recruited to the trial, would allow better exploration of their associations with morphine, so I chose to use a qualitative method alongside the 2-step trial, a concurrent nested strategy. I did not plan to combine the data obtained, but thought it possible that data obtained from the qualitative component of the study might improve our understanding of the quantitative results and perhaps also provide information about the utility of the outcome measures in the 2-step trial and the acceptability of the approach to patients.

2.4.2 Sampling strategy and recruitment of participants

I obtained ethical approval to approach both those patients choosing to participate in the trial and also those who refused participation, thus interviewing those both willing and unwilling to accept the possibility of being randomised to a Step III opioid. The nesting of the qualitative study within the pain management trial would mean that I had the opportunity to interview patients similar to those seen in day-to-day practice, with a variety of social circumstances and disease variables to allow greater confidence in the generalisability of the findings. Where possible I conducted the interviews at the second-week study visit, or as soon as possible for those not recruited.

Twenty-nine patients were approached about the interview study and eighteen participated. Of these eighteen, twelve had also agreed to participate in the 2-step trial. Five patients who entered the 2-step trial did not participate because they died soon after study entry. Six other patients were approached about the interviews but did not take part; two died very quickly and four did not want to take part (Figure 3).

Figure 3: Recruitment of participants into the interview study



2.4.3 In-depth interviews

I decided to use in-depth interviews to explore patients' concerns about morphine and other Step III opioids. Using a mixture of open and closed questions would give an opportunity to develop discussion according to the issues the participants raised and would avoid me imposing my assumptions on them. In this way, concepts and theories are derived inductively from the interviews themselves and may be different from those predicted at the start of the research process.[171] I conducted the interviews with the aid

of a topic guide (Appendix 26) in order that the same key areas were covered with each person. The first part of the interview was designed to introduce the topic and to ensure that the participant had sufficient information (Appendix 27) to give written informed consent (Appendix 28). I then asked the participants about the history of their cancer in order that the appropriate terminology for that person could be used for the remainder of the interview and to make them feel at ease with the interview process. They were then asked to describe their pain and how it impacted on their lives. The second stage of the interview focussed on the consultation at which opioids had been offered as a possible option for pain control and asked open questions about this, encouraging participants to discuss their thoughts and feelings at this time. This part of the interview was led by their responses. Further questions were asked to explore whether others in the participant's social network had an influence on their decisions regarding opioid analgesics. When all areas had been covered, the interview concluded with a rounding off question, which was usually "Was there anything else you wanted to ask or thought that I might ask you?" Throughout the interview clarification of meaning was sought and further probing questions were used in response to the conversation that was taking place. The topic guide was refined during the research process when the early participants raised further areas of interest, allowing these areas to be explored in subsequent interviews.

2.4.4 Data recording

The interviews were recorded using a cassette recorder with an external digital microphone. The recordings were professionally transcribed in full and I checked the transcripts for accuracy. I anonymised the transcripts and kept a record of pseudonyms.

2.4.5 Analysis

I analysed the data with Dr. Rachael Gooberman-Hill, a social scientist from the Department of Social Medicine at the University of Bristol, in order to improve the reliability of the analysis.[171] We used the constant comparison method described by Glaser and Strauss.[172] Using this method ensures that any resulting theory emerges from and is grounded in the data and requires that data collection and data analysis are inter-related and are occurring in a cyclical, iterative process.[173] After the initial reading of an interview, sections of text were marked with codes by both of us independently and all data relevant to that particular code were identified. In the initial analysis phase there were several overlapping codes, derived in an attempt to capture as many of the nuances in the data as possible. These initial codes with their supporting data were then displayed in charts using the methods described by Tissier[174] allowing similarly coded sections of texts from separate interviews to be compared. The codes were then discussed and refined by both of us into analytical themes, in order to summarise the phenomena under study for others. A further refinement and validation of the themes was sought by showing the charts generated by the first 13 interviews to a group of palliative care doctors and nurses during a journal club session. Throughout the analysis deviant cases were used to test and develop the themes. Once the final themes were decided upon, all of the data relevant to these themes were gathered in a descriptive account, along with a description of the participants and the impact of pain on their lives. This descriptive account "pulled together" all of the information obtained in the interviews and from it a model was developed in order to describe for others the relationships between the emergent themes. The interviews for trial participants and non-participants were analysed in a single group because initial analysis revealed that

there were no noteworthy differences between the two groups. Furthermore, both groups contained people who had commenced step III opioids by time of interview.

2.4.6 Reflexivity

It was possible that my dual role of interviewer and study doctor might have an impact on the in-depth interviews and also my analysis of them.[175] However, being aware of this meant that I took measures to minimise the risk of bias.When possible, the 2-step trial research nurse undertook the recruitment visit and the first week telephone call, minimising my contact with participants before the interview. I used impartial terminology during the interviews and encouraged participants to "tell me everything, even the bits you think I may not want to hear". The majority of the interviews were conducted in the participants' own homes. Rachael listened to the first interview as a check on style and I used the first read of all transcripts to monitor my technique. My influence on analysis is considered later in the discussion of the interviews.

2.4.7 Quality

In summary, I aimed to conduct the qualitative component of the study in as rigorous a manner as possible; maximising the generalisability of the findings by recruiting all respondents approached about the study and potentially offered Step III opioids; assuring reliability with the use of a topic guide so that all areas were covered with all informants and by collaborating with Rachael Gooberman-Hill so that the initial coding and refinement of coding was done by more than one person and in a transparent manner as described above. This collaboration also served as a safeguard that my role as a doctor did not overly influence the data generated in the interviews.

Chapter 3: Results

3.1 A survey of cancer pain control by South West England Palliative Care Teams

26 of the 32 palliative care teams approached participated in the study. Reasons for not participating at the outset included not having indemnity for research (1), censure of the questionnaire (1), lack of response (1) and no access to medical records, therefore unable to complete the professional questionnaires (1). Two further teams withdrew from the study after approvals had been obtained; one because of a change in personnel and one team citing insufficient time.

3.1.1 Palliative care services recruited

A mixture of hospital support teams and hospice services across the South West region were recruited. The teams involved covered inner-city areas, towns and rural populations. A total of 122 professionals were involved in the study, of whom the majority (95) were nurses. Patients from all settings were represented although there were very few outpatients (Table 3).

3.1.2 Number of patients recruited

A total of 298 patient questionnaires were returned. 286 patients completed the questionnaires in full and 12 patients provided demographic data only. 242 patients had pain, only eight less than the required sample size of 250. Most of the centres had over-

estimated the number of recruits they hoped to obtain. In general, if a lower number had been estimated, the more realistic that number was (Table 4).

3.1.3 Patients declining to participate

20 of the 26 participating teams provided data about the number of patients who declined the study outright. From these 20 teams, only 12 patients were shown to have declined, seven of whom came from one site. There was no obvious reason for this.

Table 3: Numbers recruited from each setting

Setting	No. of patients recruited	No. of patients with pain (%)
Hospice IPU	72	68 (94.4)
OP Clinic	9	9 (100.0)
Day hospice	61	45 (73.8)
Home	93	74 (79.6)
Hospital	50	45 (90.0)
Total*	285	241 (84%)

** data on setting missing for one patient*

Table 4: Patients recruited per centre with numbers estimated

Site number	Palliative care team setting	Numbers returned	Numbers estimated	Percentage of estimated recruits obtained
11	Hospital support team	6	10	60.0
40	Hospice	18	20	90.0
21	Hospital support team	7	15	46.7
27	Hospice	14	45	31.1
26	Hospice	13	45	28.9
13	Hospital support team	3	10	30.0
12	Day hospice	5	15	33.3
34	Hospice	3	10	30.0
35	Hospice	18	20	90.0
18	Hospital support team	4	10	40.0
17	Hospital support team and hospice	7	15	46.7
36	Hospice	43	80	53.8
30	Hospital support team	4	15	26.7
29	Hospice	26	45	57.8
10	Hospital support team	5	20	25.0
15/16	Hospital support team and hospice	17	35	48.6
19/20	Hospital support team and hospice	31	40	77.5
22/23	Hospital support team and hospice	10	10	100
24/25	Hospital support team and hospice	12	60	20.0
28	Hospital support team	10	10	100
31	Hospital IPU	5	15	33.3
32	Hospice	12	10	120
37	Hospital support team	5	15	33.3
38/39	Hospice	20	33	60.6
Total		298	603	49.4

3.1.4 Differences between patients providing pain data and patients providing demographic data only.

There were no significant differences between those patients providing pain data and those providing only demographic data in terms of age, primary tumour site, ECOG scale or the setting from which they were recruited (Table 5)

Table 5: Comparison between patients providing pain data and those providing demographic data

	Demographic data provided	Pain data provided	P value
Age in years (mean)	67.0	67.7	
N	9	284	0.85
Primary tumour site (%)			
Breast	10.0%	14.7%	
Colorectal	10.0%	15.4%	
Lung	20.0%	12.3%	
Upper GI	20.0%	11.6%	
Unknown 1^0	10.0%	2.8%	
Prostate	20.0%	19.6%	
Haematological	0.0%	3.8%	
Mesothelioma	0.0%	1.7%	
Head/neck	10.0%	2.5%	
Other	0.0%	15.4%	
N	10	285	0.62
ECOG Scale* (%)			
0	18.2%	7.8%	
1	18.2%	45.4%	
2	45.4%	23.8%	
3	18.2%	17.4%	

	Demographic data provided	Pain data provided	P value
4	0%	5.7%	
N	11	282	0.21
Setting			
Hospice IPU	27.3%	25.3%	
O/P Clinic	0.0%	3.2%	
Day Hospice	18.2%	21.4%	
Home	27.3%	32.6%	
Hospital IPU	27.3%	17.5%	
N	11	285	0.89

*ECOG Scale:0 = normal activity; 1 = symptoms but fully ambulatory; 2 = symptomatic but in bed < 50% of the day; 3 = needs to be in bed >50 % of the day but not bedridden; 4 = unable to get out of bed

3.1.5 Percentage of patients with uncontrolled pain (score of ≥ 5)

Of the 242 patients reporting pain, 79.3% (C.I. 74.1% to 84.4%) had a worst pain score of ≥ 5 or uncontrolled pain.

3.1.6 Demographic characteristics of those reporting worst pain scores of ≥ 5 versus < 5

Those with uncontrolled pain were on average 4 years younger than those with controlled pain (p = 0.04) (Table 6). There was no evidence that sex, IMD quintile, setting, ECOG performance status, or primary tumour site influenced whether or not pain was controlled. There was some weak evidence that the length of time known to the palliative care team was a factor in pain control. There was a greater percentage of patients with controlled pain (87.8% vs. 78.4%) in those patients who had been known to palliative care teams for longer than one week.

Table 6: Demographic factors in those reporting pain scores of <5 and ≥ 5

	Worst pain <5	Worst pain ≥ 5	p-value
Mean age, yrs (SD)	70.7 (11.6)	66.7 (12.2)	0.04
N	49	192	
Male (%)	49.0	42.0	
N	49	192	0.4
IMD quintile (%)			
1	8.2	10.7	
2	12.2	18.3	
3	28.6	30.2	
4	40.8	29.0	
5	10.2	11.8	
N	49	169	0.58
Setting (%)			
Hospice IPU	26.0	28.8	
O/P Clinic	6.0	3.1	
Day Hospice	26.0	16.8	
Home	30.0	30.9	
Hospital	12.0	20.42	
N	49	192	0.34
ECOG performance status* (%)			
0	6.0	4.2	
1	48.0	44.2	
2	24.0	25.3	
3	12.0	21.5	
4	10.0	5.3	
N	50	190	0.47
Primary tumour site (%)			
Breast	20.0	12.6	
Colorectal	12.0	18.3	

	Worst pain <5	Worst pain ≥ 5	p-value
Lung	12.0	10.9	
Upper GI	8.0	13.6	
Unknown 1°	0.0	3.7	
Prostate	28.0	17.8	
Haematological	4.0	3.7	
Mesothelioma	4.0	1.6	
Head/neck	0.0	2.6	
Other	12.0	15.2	
N	49	192	0.34
Time known to palliative care teams (%)			
< 24 hours	0.0	9.2	
> 24 hours but < 1 week	12.2	12.4	
> 1 week	87.8	78.4	
N	49	185	0.08

IMD = Index of Multiple Deprivation

*ECOG Scale:0 = normal activity; 1 = symptoms but fully ambulatory; 2 = symptomatic but in bed < 50% of the day; 3 = needs to be in bed >50 % of the day but not bedridden; 4 = unable to get out of bed

3.1.7 Mechanism of pain

The most frequent pain mechanisms were thought to be nociceptive and mixed pain. Pure neuropathic pain or other causes of pain such as tenesmus were rare. Nociceptive pain was caused by bone, viscera and soft tissue in equal proportions of those with nociceptive pain. There was no evidence that the mechanism of the pain was associated with uncontrolled pain, but there was strong evidence that the presence of pain flares (or breakthrough pain) was associated with poor pain control as was the frequency of these flares (Table 7).

Table 7: Effect on pain scores of pain mechanism and pain flares

	Worst pain <5	Worst pain ≥ 5	p-value
Mechanism of pain (%)			
Nociceptive	62.5	53.2	
Neuropathic	2.1	2.7	
Mixed	31.3	41.0	
Other	4.2	1.1	
N	48	188	0.32
Pain flares present (%)	59.2	87.5	
N	49	192	< 0.001
Number of flares in those with pain flares (%)			
0-3	93.1	57.1	
4-6	6.9	32.1	
7-10	0.0	6.6	
>10	0.0	4.2	
N	29	168	0.003

3.1.8 Opioid medication

15% of patients were under-medicated according to their pain management index scores but this was not a factor contributing to poor pain control. Patients with a positive pain management index were more likely to have a worst pain score of < 5. This may simply be because worst pain score contributes to the pain management index score i.e. the lower the worst pain score, the more likely the PMI is to be positive if the patient is using Step III opioids. A greater percentage of patients with uncontrolled pain used medication for breakthrough pain (rescue medication). Amongst those who used rescue medication, it was effective in a greater proportion of patients with controlled

pain (p = 0.27). More patients with uncontrolled pain were using a Step III opioid for pain control (Table 8).

Table 8: Effect of medication on pain control

	Worst pain <5	Worst pain ≥ 5	p-value
Adequately medicated (% yes)	84.0	81.6	
N	50	190	0.69
Pain management index (%)			
-3	0.0	1.1	
-2	4.0	7.9	
-1	12.0	9.5	
0	16.0	51.6	
1	34.0	29.5	
2	26.0	0.5	
3	8.0	0.0	
N	50	190	<0.001
Use rescue drugs (% yes)	71.1	85.7	
N	38	175	0.03
Rescue drugs effective (% yes)	96.2	89.2	
N	26	148	0.27
% of patients using a Step III opioid	42.0	69.6	
N	50	191	<0.001

3.1.9 Use of drugs and other treatments for pain control

The majority of the patients (66.5 %) were using a Step III opioid. Very few patients had had an anaesthetic procedure. The use of adjuvants was also less than expected (Table 9).

Table 9: Use of drugs and non-drug measures for pain control

Drug/Treatment	% of patients (n = 242)	Mean dose (range)
Step I		
Aspirin	0.8	300 mg (150 –450)
Paracetamol	43.8	4g (1 – 8)
NSAID	18.6	
Cox II inhibitor	2.9	
Total on Step I drugs	66.1	
Step II		
Buprenorphine	0.4	35mcg/hr
Codeine	9.9	180mg (32 – 240)
Coproxamol	1.2	4 tablets (2 – 8)
Tramadol	5.7	300mg (100 – 400)
Dihydrocodeine	2.1	
Codydramol	0.4	
Total on Step II drugs	19.7	
Step III		
Morphine	34.7	93mg (3-1000)
Diamorphine	2.9	95mg (5-250)
Oxycodone	13.6	96.7mg (10-480)
Hydromorphone	0.8	8mg (8)
Methadone	0.0	
Fentanyl	14.5	100mcg/hr (25-600)
Total on Step III drugs	66.5	
One or more opioid switch†	22.7	
Adjuvant drugs		
Steroids	16.9	
Anti-depressants	15.7	
Anti-convulsants	6.6	
Bisphosphonates	9.9	
Ketamine	0.0	

Drug/Treatment	% of patients (n = 242)	Mean dose (range)
Anti-cancer treatments		
Radiotherapy	30.2	
Chemotherapy	16.9	
Anaesthetic procedures		
Nerve block	1.6	
Epidural / intra-thecal block	2.9	
Other non drug measures[‡]	10.7	

[†] *The commonest reasons for an opioid switch were inadequate analgesia (23.6%), inadequate analgesia plus side effects (29%), adequate analgesia but side effects (18.2) and change of route (21.8%).* [‡]*These included TENS, relaxation, massage and breathing exercises*

Other drugs used for the treatment of pain included anxiolytics (diazepam and lorazepam), anti-spasmodics (hyoscine butylbromide, glyceryl trinitrate and mebeverine), acid suppressing drugs (omeprazole and mucaine) anti-diarrhoeals and anti-thrombotics.

3.1.10 Patients' views on pain control

239 patients answered the final question about pain control (Table 10). Of these, contrary to the results from the worst pain score, only 34 (14.2%) felt that their pain was not controlled. Those who said that their pain was not controlled had higher "pain now" scores (difference = 2.8, CI 1.9 to 3.7; p=<0.001), higher "worst" pain scores (difference = 2.0, CI 1.1 to 3.0; p=<0.001), higher "least" pain scores (difference = 1.2, CI 0.45 to 1.9; p=0.02) and higher "on average" pain scores (difference = 2.1, CI 1.4 to 2.9; p=<0.001). The factors influencing the response to this question were the frequency of pain flares and the effectiveness of rescue medication (Tables 11 and 12).

Table 10: Demographic factors in those reporting pain controlled or not controlled

	Pain controlled	Pain not controlled	p-value
Mean age, yrs (SD)	67.3 (12.1)	68 (11.9)	0.62
N	205	33	
Male (%)	42.2	47.1	
N	204	24	0.6
IMD quintile (%)			
1	11.5	0.0	
2	17.2	13.0	
3	29.7	30.4	
4	32.3	26.1	
5	9.4	30.4	
N	192	23	0.02
Setting (%)			
Hospice IPU	27.5	35.3	
O/P Clinic	2.9	5.9	
Day Hospice	19.6	11.8	
Home	31.4	29.4	
Hospital	18.6	17.6	
N	204	34	0.66
ECOG performance status* (%)			
0	4.9	2.9	
1	45.8	38.2	
2	24.6	26.5	
3	17.7	29.4	
4	6.9	2.9	
N	203	34	0.49
Primary tumour site (%)			
Breast	12.3	26.5	

	Pain controlled	Pain not controlled	p-value
Colorectal	18.1	11.8	
Lung	11.8	8.8	
Upper GI	12.3	11.8	
Unknown 1°	2.5	5.6	
Prostate	19.6	17.7	
Haematological	4.4	0.0	
Mesothelioma	2.5	0.0	
Head/neck	2.0	2.9	
Other	14.7	14.7	
N	204	34	0.46
Time known to palliative care teams (%)			
< 24 hours	7.1	9.1	
> 24 hours but < 1 week	11.6	18.2	
> 1 week	81.3	72.7	
N	198	33	0.49

IMD = Index of multiple deprivation quintile (1 is the most deprived and 5 least deprived).
*ECOG Scale:0 = normal activity; 1 = symptoms but fully ambulatory; 2 = symptomatic but in bed < 50% of the day; 3 = needs to be in bed >50 % of the day but not bedridden; 4 = unable to get out of bed

Table 11: Effect of pain mechanism and pain flares on pain control question

	Pain controlled	Pain not controlled	p-value
Mechanism of pain (%)			
Nociceptive	56.0	58.0	
Neuropathic	2.0	5.8	
Mixed	40.0	35.3	
Other	2.0	0.0	
N	200	34	0.46
Pain flares present (%)	79.9	91.2	
N	204	34	0.12
Number of flares in those with pain flares (%)			
0-3	68.7	25.8	
4-6	25.8	45.2	
7-10	3.1	19.4	
>10	2.5	9.7	
N	163	31	<0.0001

Table 12: Effect of medication on pain control question

	Pain controlled	Pain not controlled	p-value
Adequately medicated (% yes)	83.7	76.5	
N	203	34	0.30
Pain management index (%)			
-3	0.5	2.94	
-2	7.4	5.8	
-1	8.4	14.7	
0	42.4	58.8	
1	32.5	17.6	
2	6.9	0.0	
3	2.0	0.0	
N	203	34	0.11
Use rescue drugs (% yes)	84.9	74.2	
N	179	31	0.14
Rescue drugs effective (% yes)	96	52.2	
N	149	23	<0.0001
% of patients using a Step III opioid	63.7	70.6	
N	204	34	0.44

32 out of the 34 patients stating that their pain was not controlled had a worst pain score of ≥ 5 i.e. the negative predictive value of the question was 94.1%. However, 46/205 patients stating that their pain was controlled had a pain score of ≥ 5 i.e. the positive predictive value was only 22.4%.

Table 13: Comparison of answers to the single question "Is your pain controlled?" with pain scores from a numerical rating scale

"Is your pain controlled?"	Worst pain <5	Worst pain ≥ 5	Total
Yes	46	159	205
No	2	32	34
Total	48	191	239

3.2 Oxycodone for cancer-related pain: meta-analysis of randomised controlled trials

3.2.1 Search results

The search strategy yielded 104 references. After an initial read of the abstracts by two reviewers, 25 were retrieved for a more detailed analysis (reasons for not retrieving all papers are given in Figure 4). Of these 25, a further 19 studies were excluded for the following reasons: no active drug or placebo control group (n = 7); no randomisation (n = 8); data previously published (we identified replication of efficacy data from two trials contained within papers reporting on the pharmacokinetic outcomes from these studies) (n = 2); studies comparing oxycodone in combination with paracetamol (n = 2). This meant 6 trials met the inclusion criteria (Figure 4). Of these, one was a single-dose study evaluating the analgesic potency and duration of action of intra-muscular oxycodone against intra-muscular morphine and codeine and was excluded from meta-analysis. Of the remaining five reports, there were: three crossover trials comparing oral oxycodone with oral morphine; one crossover trial comparing oral oxycodone with oral hydromorphone; and one parallel group trial comparing oral oxycodone and oral morphine (Table 14).

After contacting study others or sponsors, individual patient data were obtained for the Heiskanen study. For the Bruera, Hagen and Mucci-LoRusso studies, we were provided with mean within-patient differences in pain scores (comparing the first and final study day) and an estimate of the standard deviation. Analysable data were unavailable for the Kalso study (which reported no statistically significant difference in visual analogue scale ratings between the morphine and oxycodone groups, but more

nausea with oral morphine) and the Beaver study (which demonstrated that intramuscular oxycodone was 0.68 times as potent as intramuscular morphine but had a slightly shorter duration of action). Thus four studies were included in the meta-analysis.

Figure 4: Quorum Statement flow chart

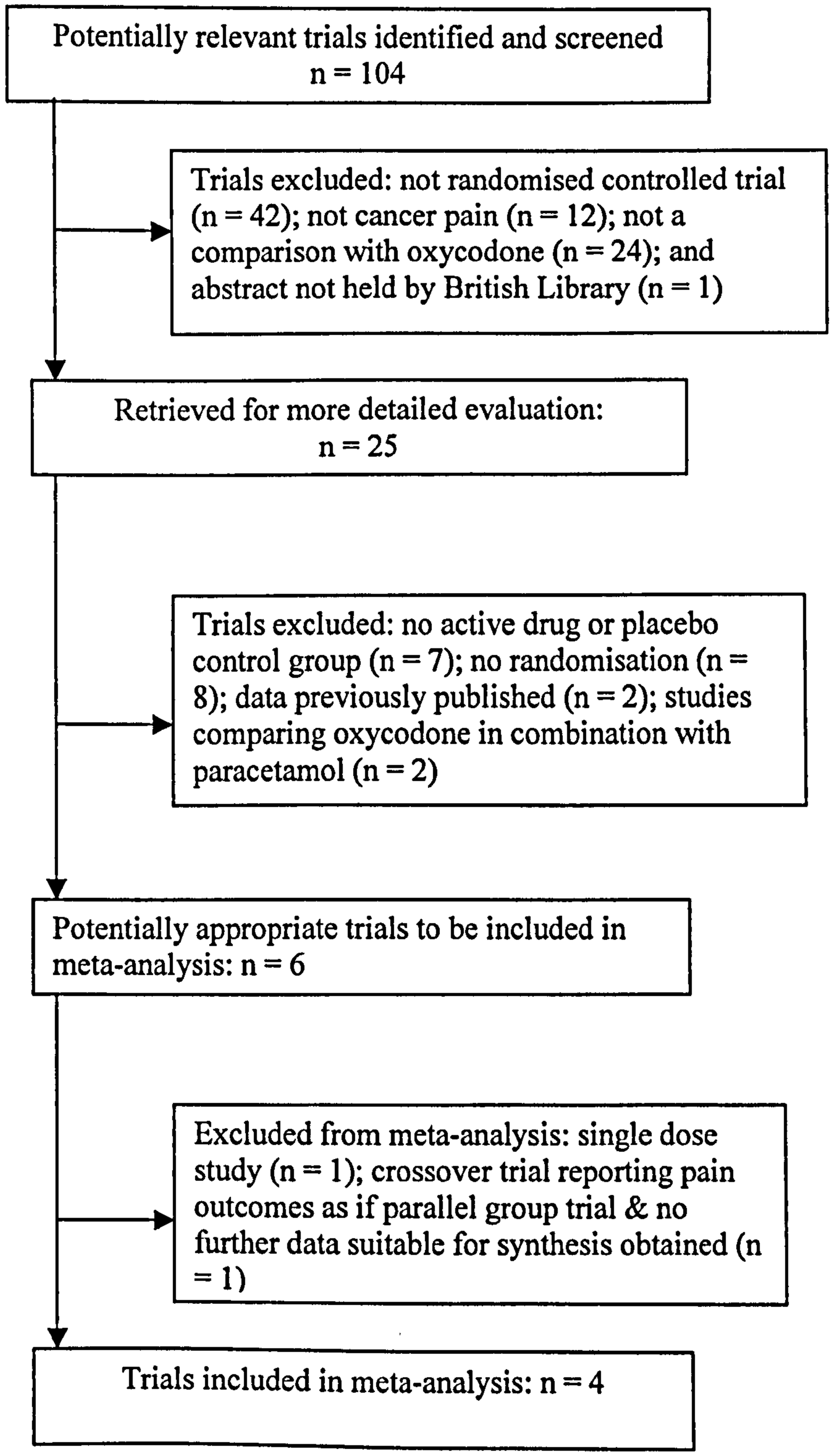


Table 14. Included studies

Study, Methods. Participants	Numbers entered, completed and withdrawals	Intervention	Outcomes reported in paper	Notes
Beaver Double blind crossover Hospitalised patients Mean age = 46 yrs	34 entered; N = 28 (completed one round of low dose and high dose for each medication) 6 withdrawals not related to study drugs	Each patient given high dose and low dose morphine (8mg, 16mg or 32mg), oxycodone (7.5mg, 11mg, 15mg, 22mg 30mg) and codeine (90mg or 180mg) **intramuscularly** on separate days.	Intra-muscular oxycodone = 0.68 times (CI 0.32-1.07) as potent as intra-muscular morphine No differences noted in side effects	Funded by research charity and pharmaceutical industry
Bruera Double blind crossover Patients with stable cancer pain (3 or more days of stable opioid doses)	32 entered N = 23 5 withdrawals due to adverse events (3 on morphine 2 on oxycodone) 4 withdrawals for other reasons.	7 days of each drug (Crossover day 8) Dose adjustments permitted until pain control achieved. Rescue dose = 10% of 24 hr dose Dose titration similar in both groups. Mean morphine dose (M) = 72.6mg 12 hourly Mean oxycodone dose (O) = 46.5mg 12 hourly	Pain measured on visual analogue scale (10cm) and categorical scale (0-4) No significant difference in pain intensity scores between treatments. No statistically significant differences in mean severity of any adverse events or in patient preference	Funded by pharmaceutical company Summary statistics provided for meta-analysis
Hagen Double blind crossover Patients with chronic stable cancer pain (3 or more days of stable opioid doses) Mean age = 56yrs	44 entered study N = 31 8 withdrawals due to adverse events (6 on oxycodone, 2 on hydromorphone) 5 withdrawals for other reasons	7 days of each drug (Crossover day 8) Dose adjustments permitted until pain control achieved. Rescue dose = 10% of 24 hr dose Dose titration similar in both groups Mean hydromorphone dose = 30mg in 24 hrs Mean oxycodone dose = 124mg in 24 hrs	Pain measured on visual analogue scale (10cm) and a 5 point categorical scale (0-4) Overall mean pain intensity across all days: **VAS:** 28mm (CR oxycodone) and 31mm (CR hydromorphone) p=0.1 **CAT:** 1.4 (CR oxycodone) and 1.5 (CR hydromorphone) p=0.096. Nausea and sedation measured on a 10cm visual analogue scale. No significant differences in nausea or sedation scores or patient preference between groups.	Funded by pharmaceutical company Summary statistics provided for meta-analysis

Study, Methods. Participants	Numbers entered, completed and withdrawals	Intervention	Outcomes reported in paper	Notes
Heiskanen Double blind crossover Patients with chronic stable cancer pain Mean age = 60yrs	45 entered study N = 27 7 discontinued due to adverse events (5 on oxycodone 2 on morphine) 11 discontinued for other reasons	Initial open label dose titration phase until 48hours of effective pain relief, followed by crossover sequences lasting 3-6 days Rescue dose = 1/6-1/8 of 24hr dose Dose titration similar in both groups Mean morphine dose (M) = 180mg in 24hrs Mean oxycodone dose (O) = 123mg in 24 hrs; M:O = 1.5	Pain measured on 4 point verbal rating scale When the stable phases were combined, pain control was better with CR morphine than with CR oxycodone. Constipation more common with oxycodone Vomiting more common with morphine Nigh-time acceptability better in the morphine group	Assistance from pharmaceutical company Individual patient data obtained
Kalso Double blind crossover Patients with cancer pain not controlled on opioids for mild to moderate pain Mean age = 52yrs	20 entered the study N = 19 1 withdrawal due to adverse events on morphine	Patients titrated to pain-free using a Patient Controlled Analgesia device with either morphine or oxycodone for 48hrs Then switched to oral dose (calculated from previous oral consumption) of same drug for 48hrs. Protocol repeated with the other drug for next 96hrs. Mean morphine dose (M) = 204mg in 24 hrs Mean oxycodone dose (O) = 150mg in 24 hrs	Pain measured on a visual analogue scale (10cm) Pain scores from last 24 hours of each of the four stages used in statistical analyses No statistically significant differences in pain scores between groups. Oral morphine caused more nausea.	Funded by research charity No further data obtained
Mucci-LoRusso[148] Double blind parallel group Patients with chronic cancer pain requiring 30-340mg oxycodone or equivalent Mean age = 59yrs	101 entered N = 79 9 discontinued due to adverse events (3 on oxycodone, 6 on morphine). 12 discontinued for other reasons. One patient did not receive any medication.	Initial doses of study medication were calculated from pre-study opioid requirements. Dose titrated up until stable pain control for 48hrs Mean morphine dose (M) = 140mg in 24 hrs Mean oxycodone dose (O) = 101mg in 24 hrs Rescue dose = 1/6-1/8 of 24hr dose	Pain on a 4 point categorical scale (0-3) Reduction in mean pain scores of 0.6 from baseline in both groups; o statistically significant difference between treatments noted No difference in quality of life (FACT-G) scores or patient preference between groups	Funded by pharmaceutical company Summary statistics provided for meta-analysis

3.2.2 Methodological quality of included studies

Only one trial (Heiskanen) reported on the method of concealment of allocation to treatment (the randomisation code was kept by the hospital pharmacist), although information about whether or not restricted randomisation was used in generating the allocation sequence was not available in the trial report (Table 15). All of the trials used matched placebo tablets to blind both the patient and the clinician. No studies indicated whether or not analysis by intention-to-treat was undertaken. In all included trials, patients who withdrew from the study for any reason were excluded from the final analyses reported in the paper. The numbers who withdrew from each trial were as follows: Bruera (32 entered; 9 withdrawals); Hagen (44 entered, 13 withdrawals); Heiskanen (45 entered, 18 withdrawals); Mucci LoRusso (101 entered, 22 withdrawals) (Table 15). None of the publications reported on whether or not the outcome assessor was blind to treatment. Each trial reported that patients in both treatment groups had their opioids titrated in a similar manner until stable doses were obtained. The trials were of short duration, lasting between 10 and 20 days.

Table 15 : Methodological quality of trials included in the meta-analysis

Trial	Generation of the allocation sequence	Method of allocation concealment	Masking		Intention-to-treat analysis
			Patients / clinicians	Outcome assessors	
Hagen[77], 1997	Not reported	Not reported	Matched placebo tablets used	Not reported	Not reported
Heiskanen[75], 1997	Computer generated; unclear if restricted randomisation was used	List of codes held by hospital pharmacist	Matched placebo tablets used	Not reported	Not reported
Bruera[74], 1998	Not reported	Not reported	Matched placebo tablets used	Not reported	Not reported
Mucci-LoRusso[148], 1998	Block randomisation in nine separate centres	Not reported	Matched placebo tablets used	Not reported	Not reported

3.2.3 Pain intensity scores

3.2.3.1 Summary pain scores

Table 16: Summary pain scores obtained from Napp Pharmaceuticals for included studies

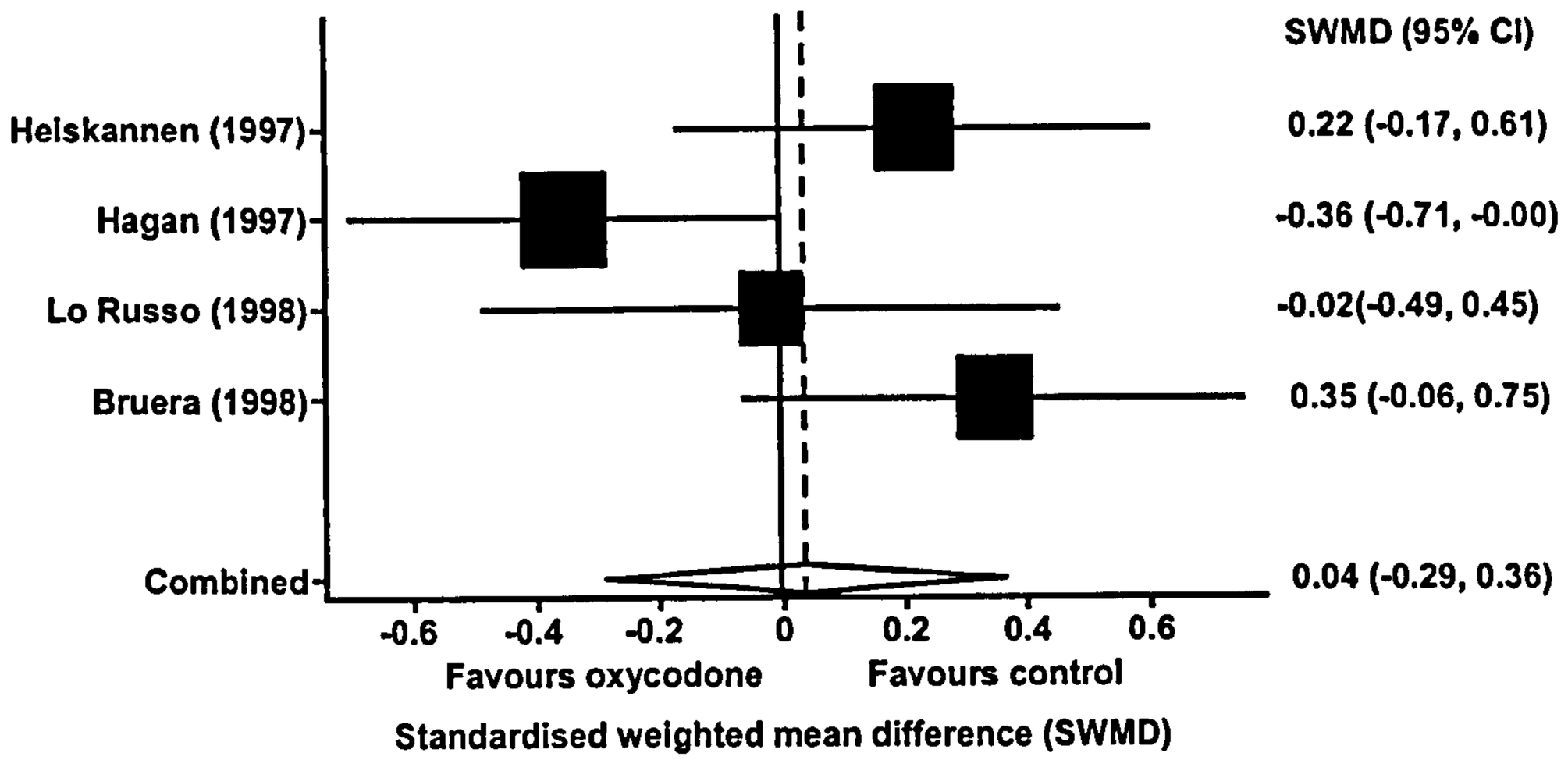
Trial	Mean scores on oxycodone	Mean scores on control	Mean Difference	Standard error
Hagen	25.21	27.68	-2.47	1.57
Bruera	28.34	24.73	3.61	2.74
Mucci-LoRusso	19.56	19.98	-0.42	5.35
Heiskanen	0.88	0.73	0.15	0.18

3.2.3.2 Pooled scores

In pooled analyses, there was no evidence that mean pain scores differed between oxycodone and control groups (mean difference in standardised pain scores = 0.04; 95% CI: -0.29 to 0.36; p =0.8) (Figure 5). There was evidence of heterogeneity between the study estimates (I^2 = 62%, heterogeneity p = 0.05). The pooled standardised difference in pain scores for the 3 studies that compared oxycodone with morphine was 0.20 (-0.04 to 0.44; I^2 = 0%) and the standardised difference for the study that compared oxycodone with hydromorphone was -0.36 (-0.71 to 0.00) (p for difference in effect estimates = 0.1). Based on the pooled standardised differences we observed and the standard deviations observed in the individual trials, we estimate that

for oxycodone compared with morphine or hydromorphone, the pooled standardised differences represent only 2-3 mm on a 100mm visual analogue scale.

Figure 5: Standardised weighted mean differences (95% confidence intervals) in pain intensity scores in patients with cancer, comparing oxycodone minus control in all four trials with analysable data.



The results of other outcomes described in the included papers are detailed in Table 14.

In summary, no differences in patient preference or quality of life were demonstrated, although the Heiskanen study suggested that night-time acceptability of morphine was better than oxycodone. As different measures were used and the results were not reported in sufficient detail, they could not be combined in meta-analyses.

3.2.4 Side effects

The point estimates for the pooled odds ratios comparing oxycodone with control were 0.75 (95% C.I. 0.51-1.1) for nausea and 0.72 (95% C.I. 0.49-1.06) for vomiting (Table 17). There was no evidence for any differences between oxycodone and morphine in any of the side effects examined within the trials. There was substantial evidence of heterogeneity in estimates of the association of oxycodone with dry mouth and drowsiness (I^2 = 73.7% and 71.4%, respectively). When the meta-analysis was repeated using only data from the trials with morphine as control, both pooled odds ratios favoured oxycodone (dry mouth: odds ratio = 0.56; 95% CI: 0.38 to 0.83; drowsiness: odds ratio = 0.72; 95% CI 0.47 to 1.1).

3.2.5 Adverse events

Overall, the discontinuation rate due to adverse events was 13% (29/222) when data from all studies were combined; as many as 90% experienced opioid-related side effects in each trial (Table 18). Discontinuation rates due to adverse events were similar in oxycodone and control groups.

Table 17: Pooled odds ratios for side effects recorded in the studies

Side effect	Estimated odds ratio (95% CI)						
	Bruera	**Heiskanen**	**Hagan**	**Mucci-Lo Russo**	**Random effects pooled estimate**	**Heterogeneity p-value**	**I^2**
Nausea	0.43 (0.19-0.99)	0.76 (0.33-1.77)	1.00 (0.54-1.87)	0.77 (0.35-1.70)	0.75 (0.51-1.10)	0.47	0%
Constipation	0.83 (0.31-2.19)	0.81 (0.46-1.43)	1.69 (0.92-3.13)	2.04 (0.84-4.97)	1.22 (0.76-1.95)	0.18	39%
Drowsiness	0.72 (0.38-1.36)	0.65 (0.29-1.43)	4.12 (1.55-10.97)	1.25 (0.54-2.92)	1.18 (0.56-2.50)	0.01	71%
Difficulty concentrating	0.86 (0.64-1.15)	1.00 (0.23-4.32)	1.28 (0.71-2.28)		0.93 (0.72-1.21)	0.49	0%
Hallucinations	1.55 (0.66-3.60)	1.00 (0.06-17.15)	3.19 (0.30-33.94)	0.26 (0.01-5.95)	1.46 (0.69-3.07)	0.64	0%
Dry mouth	0.54 (0.27-1.05)	0.59 (0.32-1.08)	1.87 (1.04-3.35)	0.54 (0.24-1.21)	0.77 (0.40-1.46)	0.01	74%
Vomiting	0.34 (0.07-1.59)	0.72 (0.46-1.15)	0.86 (0.40-1.86)		0.72 (0.49-1.06)	0.57	0%
Agitation	1.93 (0.71-5.26)	2.05 (0.27-15.51)	1.00 (0.67-1.49)		1.12 (0.78-1.61)	0.41	0%
Dizziness	0.46 (0.21-0.99)	1.14 (0.58-2.25)	1.80 (0.91-3.56)	0.59 (0.24-1.47)	0.89 (0.48-1.66)	0.04	63%
Poor sleep	1.17 (0.59-2.31)	1.00 (0.06-17.15)	0.48 (0.25-0.91)	2.25 (0.14-36.92)	0.79 (0.42-1.48)	0.25	27%
Twitching	1.36 (0.65-2.85)	*	1.16 (0.49- 2.76)		*	0.67	0%
Fatigue	1.00 (0.50-2.00)	2.05 (0.17-24.52)	0.72 (0.29-1.79)		0.92 (0.54-1.58)	0.69	0%
Itch	0.85 (0.41-1.75)	1.00 (0.52-1.91)	1.44 (0.86-2.43)	0.98 (0.37-2.57)	1.12 (0.80-1.56)	0.65	0%
Dreams	1.26 (0.46-3.46)	0.49 (0.04-5.84)	1.31 (0.57-3.05)		1.21 (0.65-2.27)	0.76	0%
Headache	1.407 (0.55-3.59)	1.00 (0.23-4.31)	0.54 (0.27-1.09)	1.90 (0.43-8.40)	0.93 (0.51-1.68)	0.28	22%
Sweating	1.36 (0.65-2.83)	1.12 (0.58-2.15)	0.78 (0.39-1.57)	1.09 (0.15-8.03)	1.05 (0.71-1.56)	0.75	0%

Table 18: Percentage of completers experiencing opioid side effects during studies

	Oxycodone				Morphine			Hydromorphone
	Heiskanen[75]	Bruera[74]	M-L[148]	Hagen[77]	Heiskanen[75]	Bruera[74]	M-L[148]	Hagen[77]
Nausea	53	56	42	64	53	74	48	68
Vomiting	31	9	0	26	35	22	2	29
Constipation	53	70	35	74	49	70	21	61
Dry mouth	35	74	33	74	47	83	48	68
Drowsiness	49	87	31	90	57	87	31	61
Dizziness	20	39	21	35	24	56	31	26
Difficulty concentrating	4	52	NR	58	4	56	NR	55
Fatigue	2	83	NR	77	0	83	NR	55
Poor sleep	0	65	2	39	0	56	2	55
Vivid dreams	2	26	NR	39	0	22	NR	32
Hallucinations	0	30	0	0	0	17	4	6
Headache	4	43	10	39	4	30	6	55
Agitation	0	70	NR	32	2	52	NR	32
Twitching	2	48	NR	29	2	35	NR	29
Itching	22	35	20	55	24	43	21	45
Sweating	35	61	4	55	31	48	4	61

3.3 The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

3.3.1 Recruitment

Recruitment re-commenced in December 2004 and closed at the end of November 2005 in Bristol and at the end of February 2006 in Edinburgh and Nottingham. 20 patients were recruited in total, 17 of whom were recruited from Bristol at a rate of 1-2 per month (Figure 6).

Figure 6: Flow of participants through the trial when funded by CRUK

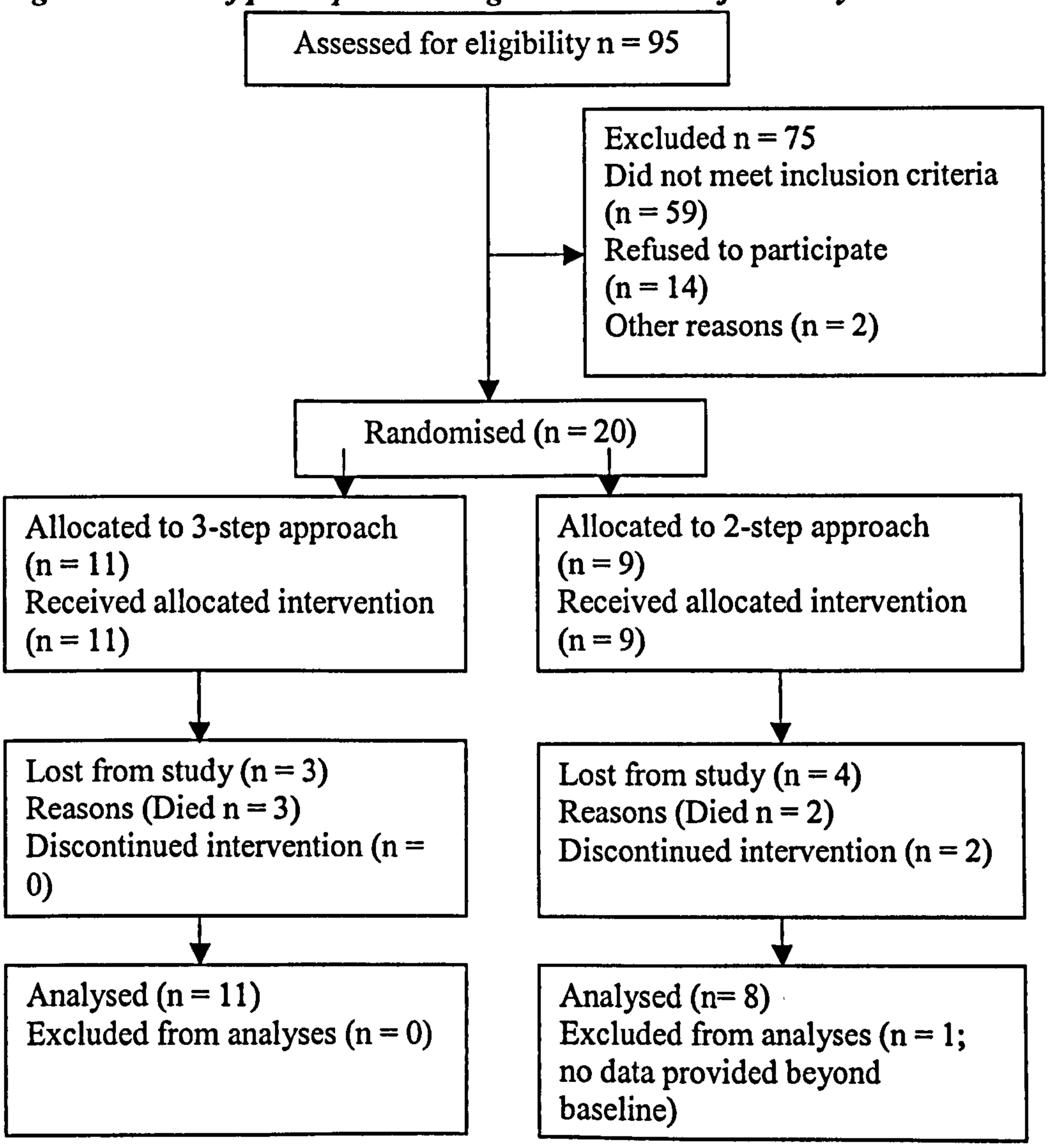
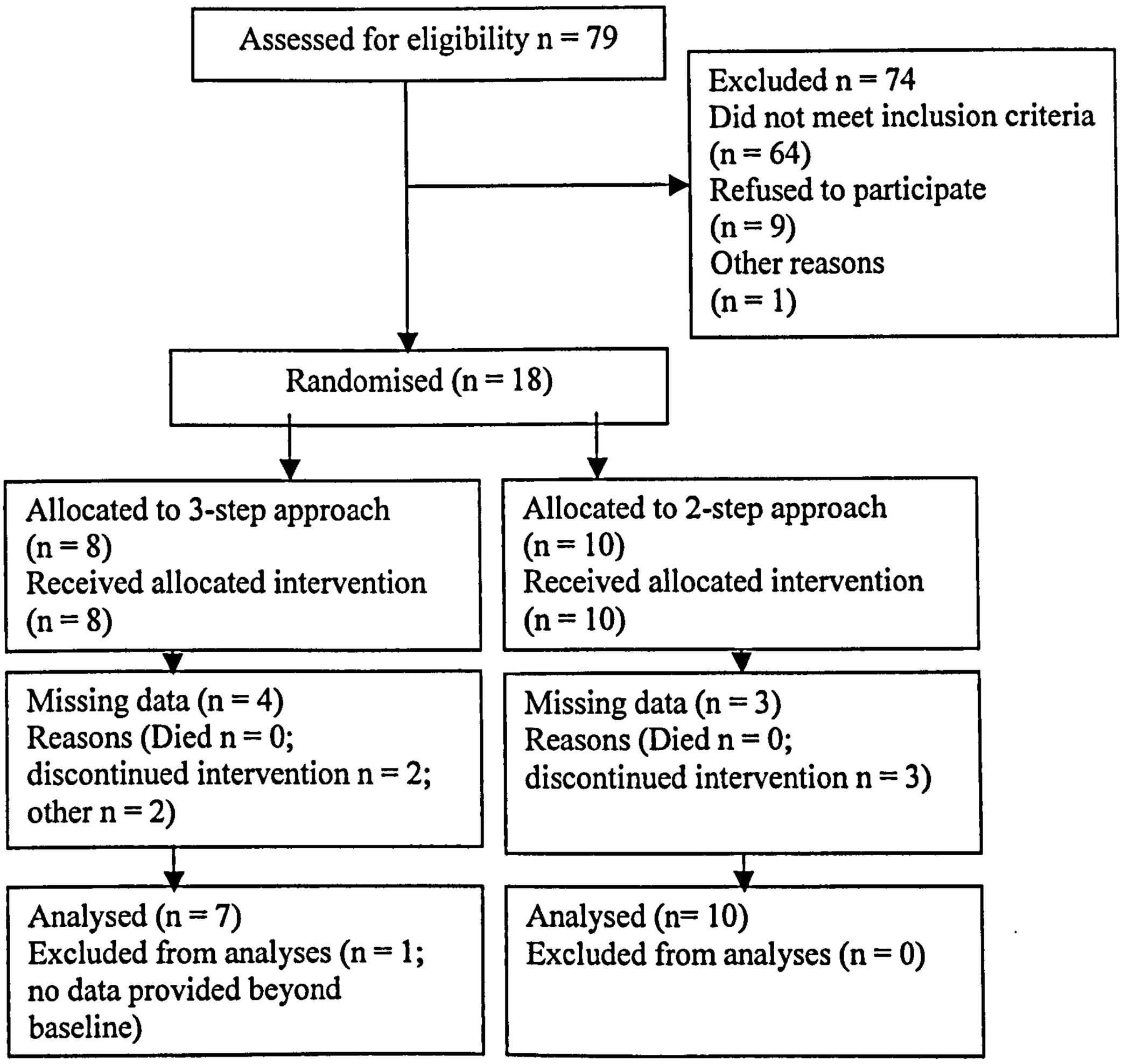


Table 19: Bristol recruitment figures

Setting	Numbers approached	Numbers recruited
St. Peter's Hospice	8	4
BHOC	33	13
Primary care	2	0
Total	43*	17

*Information about setting is missing on 6 patients

Figure 7: Flow of participants through the trial when funded by Napp



3.3.2 Extra contacts during the study period

The mean number of extra contacts during the first four weeks of the study for the study participants recruited in Bristol was 3 (range 0 – 9). The majority of these contacts were related to either pain control or adverse events.

3.3.3 Attrition rates

19 patients in the CRUK funded study provided data for the primary outcome measure. 17 patients in the Napp funded study provided data for the primary outcome measure. These 36 patients provided a total of 825 daily pain scores, the average number of observations per participant being 23 (out of a possible 28). The minimum number was 2 and the maximum was 28.

3.3.4 Second step analgesics used

A variety of second step analgesics were used for the 8 patients randomised to the 3-step approach during the Napp sponsored study (Table 20). Only 1 of these patients had received a Step III opioid by the end of the 28 days. During the CRUK sponsored study, all 10 patients were initially given co-codamol 30/500. Only 3 of these patients remained on this at the end of the 28 days. Four patients had required a Step III opioid and the remaining three patients had died.

Table 20: Choice of second step analgesics during Napp sponsored study

Patient ID	Drug used	Drug in use at 28 days
00001	Paracetamol and codeine	Step III opioid
00009	Paracetamol and codeine	NSAID
00026	Dihydrocodeine	Buprenorphine
00044	Tramadol	Tramadol
00045	Tramadol	Tramadol
00046	Tramadol	Tramadol
00049	Paracetamol and codeine	Paracetamol and codeine
00081	Paracetamol and codeine	Discontinued

3.3.5 Descriptive statistics

The following results considered the two studies as one and 19 patients were initially allocated to each group. Both groups had similar baseline pain scores at study entry (see table 21). There was no evidence of a difference in age ($p = 0.3$), sex ($p = 0.2$) or primary tumour ($p = 0.6$) between the two groups.

Table 21: Baseline characteristics of participants

		3-step approach (n = 19)	2-step approach (n = 19)
Mean baseline pain score (SD)		4.8 (2.0)	5.2 (2.2)
Age (yrs)		67.5	65.3
Sex		M = 10	M = 6
Primary tumour	Lung	2	3
	Breast	5	5
	Prostate	3	3
	Colon	3	3
	Gynaecological	0	3
	Bladder	1	0
	Unknown	1	1
	Haematological	2	0
	Sarcoma	1	1
	Stomach	1	0
Mean number of days with pain data (SD)		21.1 (10.2)	22.3 (8.9)
Stratum n = (%)	BHOC	9 (50.0)	8 (44.4)
	Nottingham	1 (5.3)	0 (0)
	Edinburgh	1 (5.3)	1 (5.3)
	Napp U.K.	1 (5.3)	4 (21.1)
	Napp Spain	7 (36.8)	6 (31.6)

3.3.6 Primary analyses

The primary analyses were:

i). To examine the difference in proportion of time in the first 28 days of the study that patients recorded a pain score of ≤ 4, using linear regression models to adjust for the effects of stratum and baseline pain score.

ii). To examine the probability of patients in both approaches having controlled pain (≤ 4) on any given day using logistic regression, taking into account the hierarchical nature of the data (up to 28 days of pain scores are clustered within an individual).

Table 22: The proportion of time spent in the first 28 days of the study with a pain score of 4 or less

Mean % of days with a pain score of ≤ 4 (SD)		Crude difference	Adjusted difference†	Fully adjusted difference*	Fully adjusted 95% CI*	Fully adjusted p value*
3-step approach	2-step approach					
59.8 (34.6)	70.6 (34.2)	10.8	16.6	16.9	-4.1 to 38.0	0.11

† adjusting for stratum
**adjusting for baseline pain scores and stratum*

These results favour the 2-step approach, showing a greater proportion of days with controlled pain in the 2-step approach but there is little statistical evidence to support them. The confidence intervals are wide and also consistent with a lesser proportion of controlled pain days in the 2-step approach.

Table 23: The odds of having controlled pain on any given day in the 2-step approach compared to the 3-step approach

Odds Ratio (OR) for controlled pain on any given day on 2-step approach compared to 3-step approach				
Crude OR	**Adjusted† OR**	**Fully adjusted* OR**	**Fully adjusted 95% CI***	**Fully adjusted p value***
1.7	3.3	2.7	0.7 to 10.5	0.15

† adjusting for stratum

**adjusting for baseline pain scores and stratum*

The fully adjusted model favoured the 2-step approach but there was little statistical evidence to support this finding and the confidence intervals were consistent with both a beneficial and detrimental effect of the 2-step approach. The effect of funder was also important when added to the regression models, showing a magnitude of effect of similar order to that of treatment (OR = 2.2; 95% C.I. 0.5 to 8.9, p = 0.29).

3.3.6.1 Imputations for missing data

Repeating the analyses with imputations for missing data did not alter the results for the primary outcome measures (data not shown).

3.3.6.2 Weighting according to the amount of data provided by each patient

The difference in the proportion of days with controlled pain did not alter significantly when the data were weighted according to the methods described in the previous chapter, although the confidence intervals were narrower (difference in proportions, fully adjusted model = 18.7, C.I. –1.2 to 38.6; p = 0.065).

3.3.7 Secondary analyses

3.3.7.1 Mean pain scores during the study period

The overall mean pain score in participants randomised to the 3-step approach was 4.0 (SD 1.9) and was 3.4 (SD 2.1) in the 2-step approach (Table 24). The fully adjusted difference indicates a lower mean pain score of 1.0 points in the 2-step approach. Whilst the 95% confidence interval is wide and includes the null, it is consistent with the possibility of a clinically significant lower mean pain score (-2.1) and excludes a clinically significant deleterious effect.

Table 24: Mean pain scores for the first 28 days for the 2-step approach compared to 3-step approach

Mean daily pain score in first 28 days (SD)						
3-step	**2-step**	**Unadjusted difference**	**Adjusted difference†**	**Fully adjusted* difference**	**Fully adjusted 95% CI**	**Fully adjusted p value**
4.0 (1.9)	3.4 (2.1)	-0.6	-0.9	-1.0	-2.1 to 0.1	0.07

† adjusting for stratum
**adjusting for baseline pain scores and stratum*

The fully adjusted difference in mean pain scores did not alter when the regression coefficient was weighted for amount of data provided (i.e. number of days pain data were provided) by each patient (fully adjusted weighted mean difference = -1.2; 95% CI = –2.2 to –0.2, p = 0.02).

3.3.7.2 Interaction by source of funding

The difference in mean proportion of days with a score of ≤ 4 was 3.2 for the two-step minus the 3-step approach in the NAPP study, and was 24.2 in the CRUK study (i.e. a crude difference in effect-size between the two funding sources of 21.0 [= 24.2-3.2]) (Table25). The difference in effect size observed in the CRUK funded study minus the NAPP study, adjusted for baseline pain score, was only 8.0 (95% CI = -32.3 to 48.2) and there was no statistical evidence of interaction by source of funding (p for interaction = 0.69). The statistical power of the test for interaction is low, however, and must be interpreted with caution.

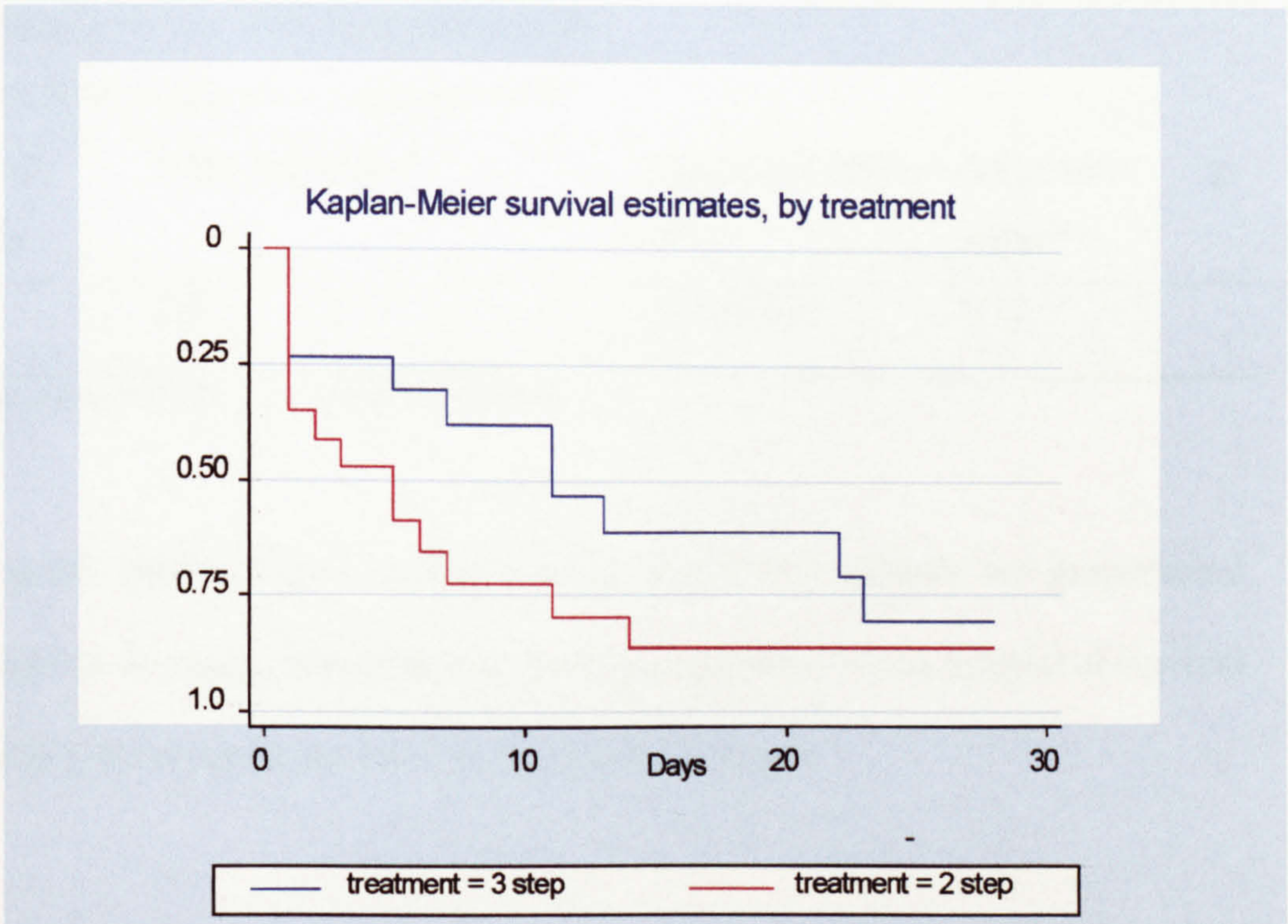
Table 25: The proportion of time spent in the first 28 days of the study with a pain score of 4 or less by source of funding

Source of funding	Treatment	Mean proportion of days with score of ≤ 4 (SD)	Difference in mean proportion of days with a score of ≤ 4
NAPP	3-step	53.6 (30.9)	3.2
	2-step	56.8 (40.0)	
CRUK	3-step	63.7 (37.7)	24.2
	2-step	87.9 (13.5)	

3.3.7.3 Time to stable pain control

There was evidence that stable pain control was achieved more quickly in the 2-step approach (mean 7.1 days SD = 8.7) compared to the 3-step approach (mean 10.8 days SD 9.8). This is demonstrated in the Kaplan-Meier curve below (Figure 8).

Figure 8: Kaplan Meier survival estimates by 2-step vs. 3-step approach



82.4% of patients in the 2-step approach achieved stable pain control compared to 64.7% in the 3-step approach. However, the p value of 0.24 (derived from the chi-square statistic from a two by two table) was consistent with there being no difference between the 2 groups. In a Cox proportional hazards model (Table 26), the fully adjusted hazard of achieving stable pain control was 100% greater (95% CI = -20% to 360%) using the two-step versus the three-step approach. The p-

value provides only weak evidence, however, in support of this finding (Cox survival analysis p value = 0.12), which must therefore be interpreted with caution.

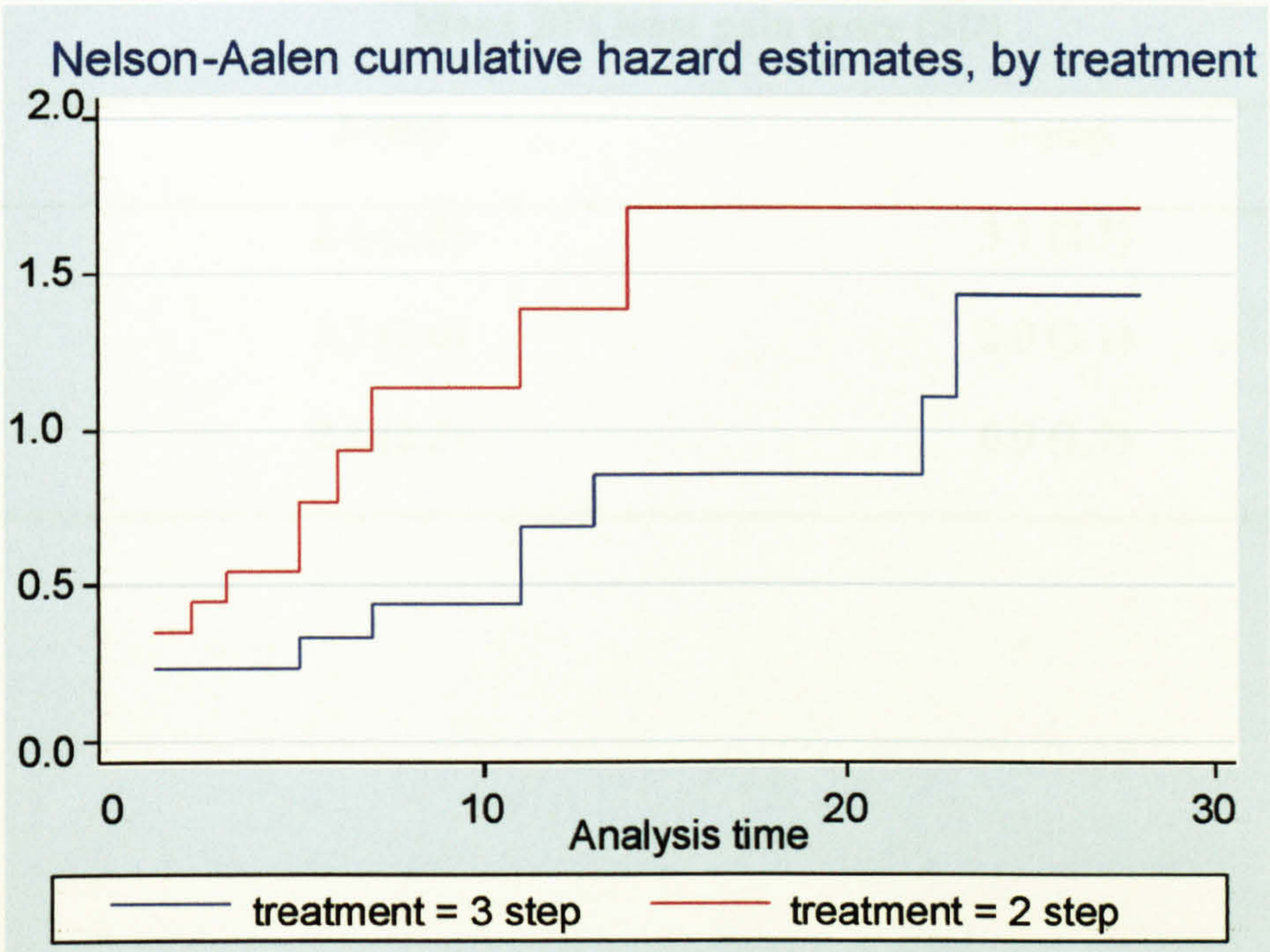
Table 26: Hazard of achieving stable pain control on 2-step approach vs. 3-step approach

Hazard ratio for achieving stable pain control on 2-step vs. 3-step approach			
Crude ratio	**Adjusted ratio***	**Adjusted 95% CI***	**Adjusted p-value***
1.7	2.0	0.8 to 4.6	0.12

**adjusting for baseline pain scores and stratum*

The graph below (Figure 9) demonstrates that Cox's hazards are proportional throughout the study, indicating that the key assumption of this method of survival analysis ("the proportional hazards assumption") is met.

Figure 9: Nelson Aalen estimates by 2-step vs. 3-step approach



3.3.7.4 Brief Pain Inventory Scores

All mean BPI scores at weeks 2 and 4 were averaged in order to compare the scores in the two approaches. All of these mean pain scores were less on the 2-step approach (tables 27-31 and figures 10-13).

Table 27: Mean BPI Least Pain Scores

	Mean BPI least pain score (SD)	
	3-step	**2-step**
Day 0	2.8 (2.8)	3.1 (2.5)
Week2	2.3 (2.6)	2.0 (3.1)
Week 4	2.1 (2.2)	0.9 (1.7)

Figure 10: Mean BPI Least pain scores over time in the 2-step approach compared to the 3-step approach

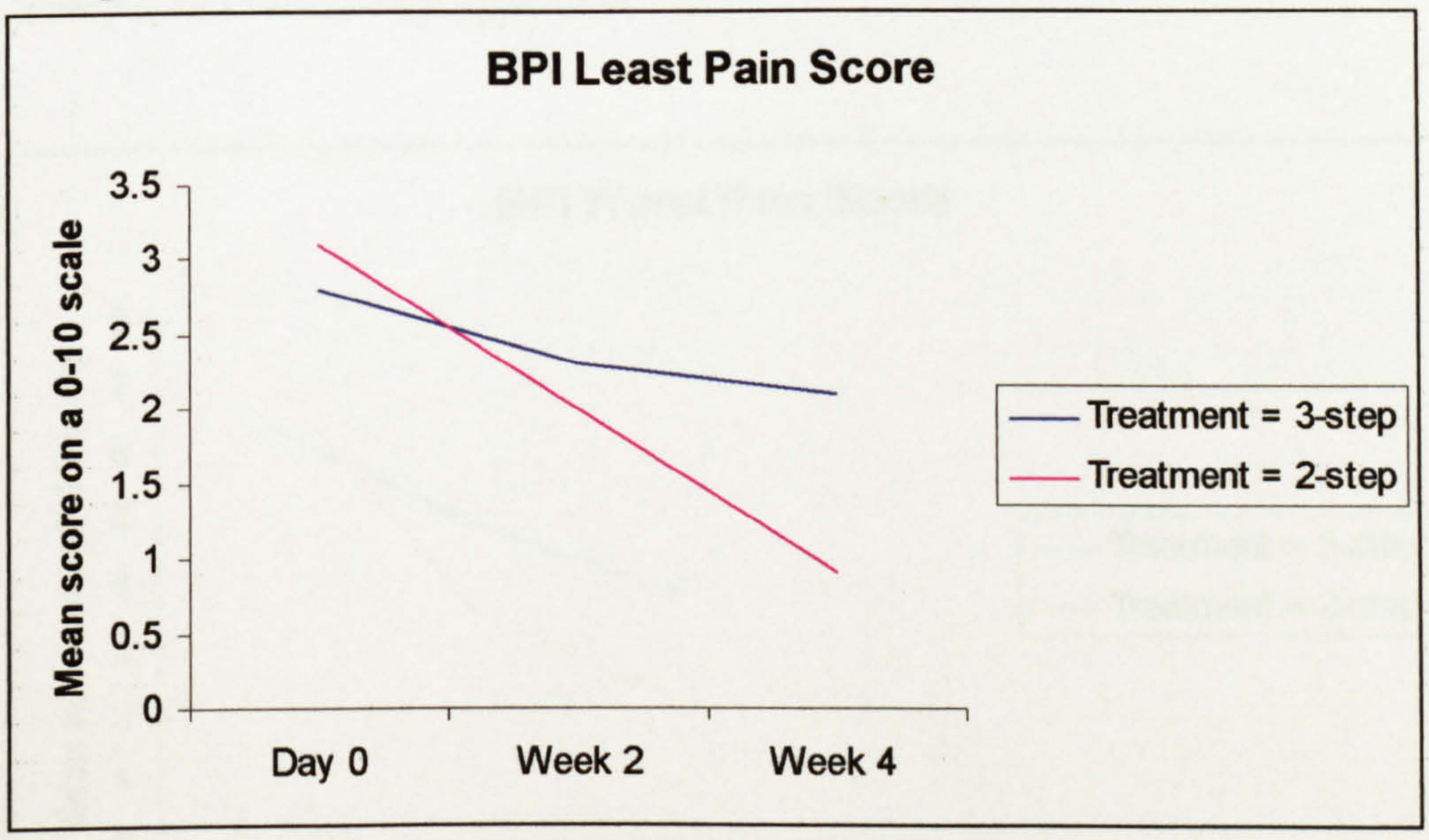


Table 28: Mean BPI Worst Pain Scores

	Mean BPI worst pain score (SD)	
	3-step	**2-step**
Day 0	6.4 (2.6)	7.3 (1.5)
Week2	4.8 (2.6)	3.6 (2.6)
Week 4	3.8 (2.8)	2.1 (3.0)

Figure 11: Mean BPI Worst pain scores over time in the 2-step approach compared to the 3-step approach

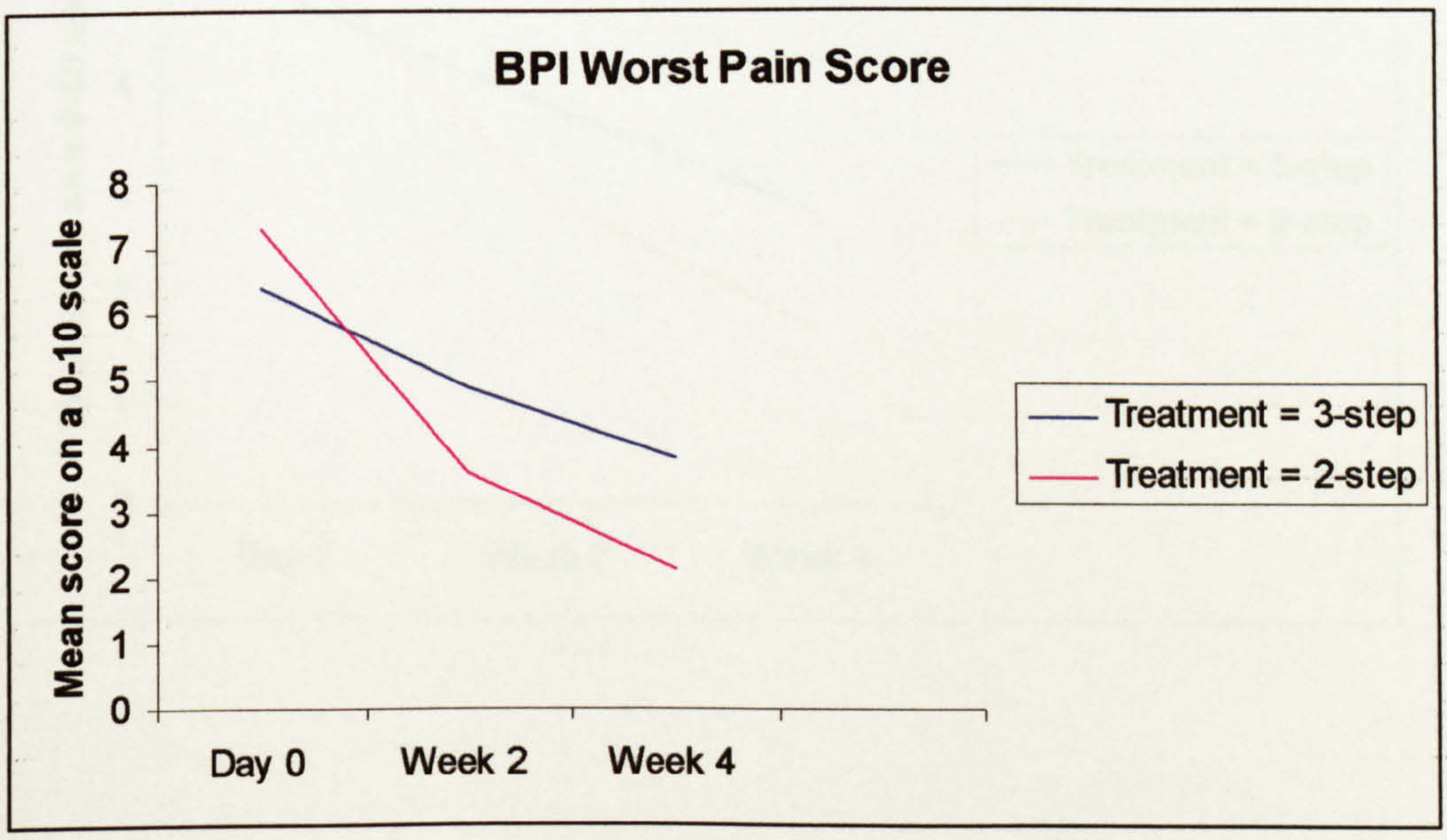


Table 29: Mean BPI Average Pain Scores

	Mean BPI average pain score (SD)	
	3-step	**2step**
Day 0	4.8 (2.0)	5.2 (2.2)
Week2	3.8 (2.6)	2.9 (2.6)
Week 4	2.8 (2.4)	1.7 (2.0)

Figure 12: Mean BPI Average pain scores over time in the 2-step approach compared to the 3-step approach

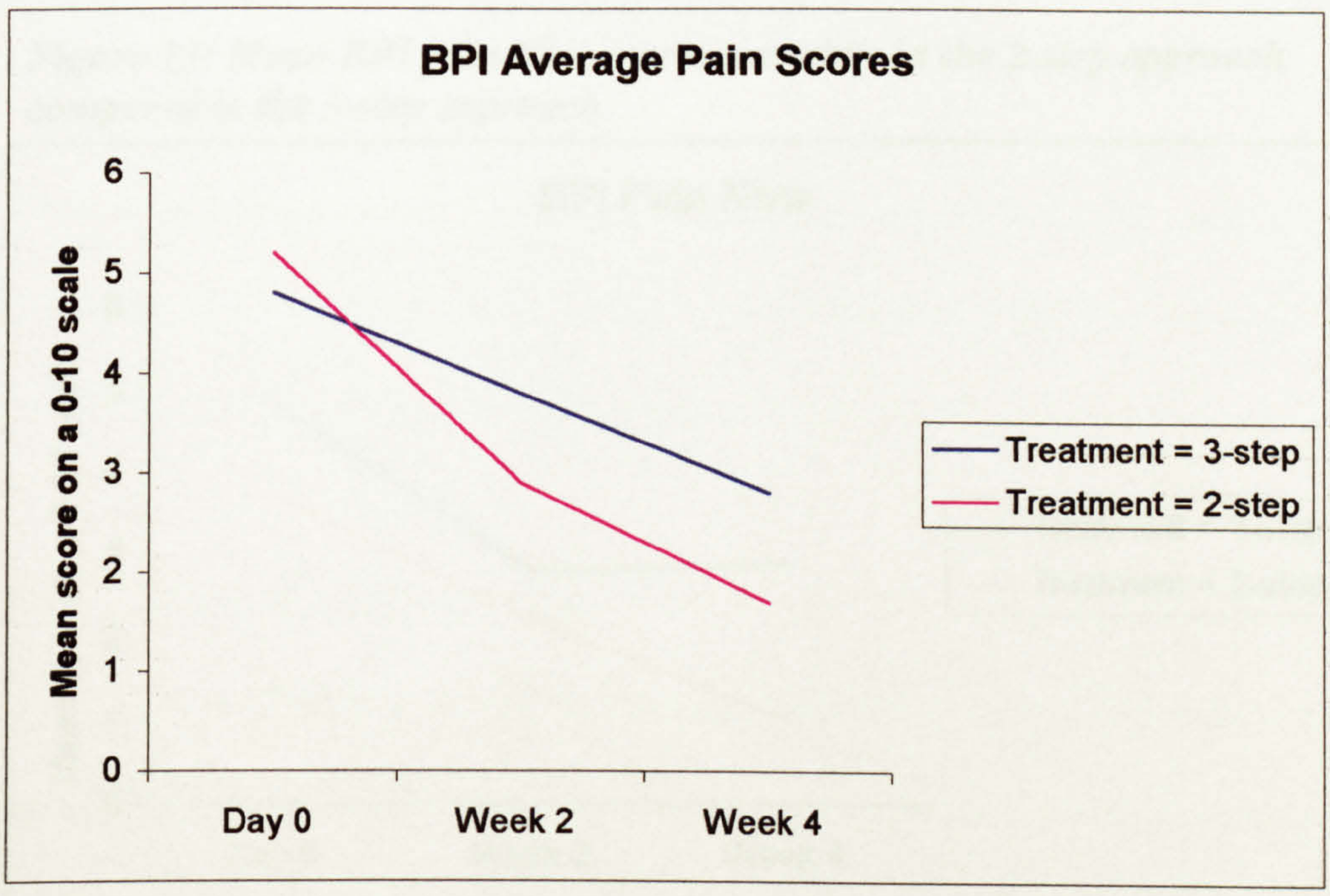


Table 30: Mean BPI Pain Now Scores

	Mean BPI pain now score (SD)	
	3-step	**2-step**
Day 0	4.6 (3.2)	3.6 (2.4)
Week2	2.6 (2.9)	2.0 (2.9)
Week 4	2.7 (2.9)	0.9 (1.5)

Figure 13: Mean BPI pain Now scores over time in the 2-step approach compared to the 3-step approach

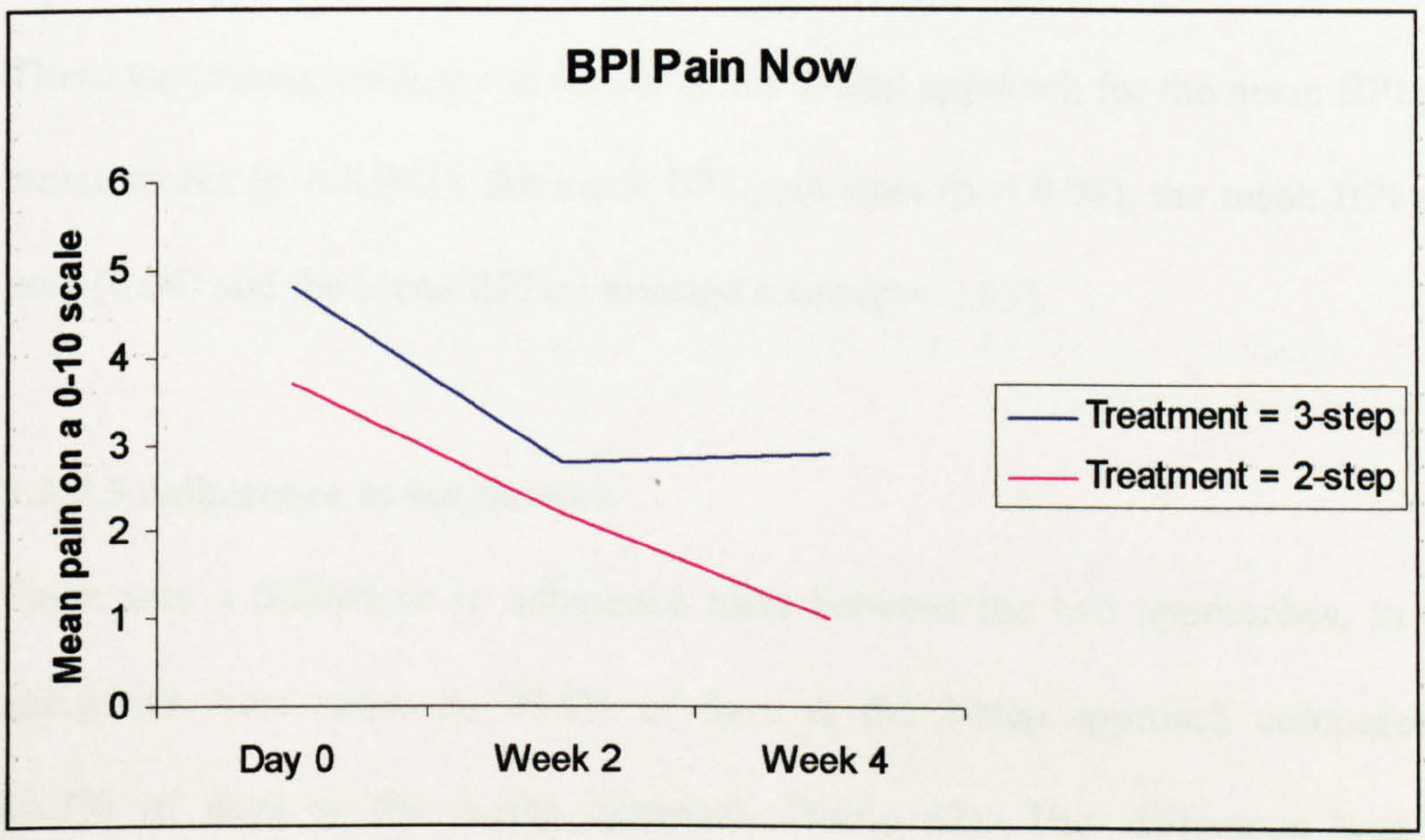


Table 31: Differences in mean BPI scores comparing the 2-step vs. the 3-step approach

	Unadjusted difference in mean score	Adjusted* difference in mean score	Adjusted 95% CI	Adjusted p value
BPI pain worst	-1.4	-2.3	-3.8 to -0.8	0.003
BPI pain least	-0.7	-1.1	-2.4 to 0.2	0.08
BPI pain average	-1.0	-1.4	-2.7 to -0.2	0.03
BPI pain now	-1.1	-1.5	-3.0 to 0.1	0.06
BPI overall interference score	-0.9	-0.9	-2.9 to 1.1	0.4

* adjusted for baseline BPI scores and centre

There was strong evidence in favour of the 2-step approach for the mean BPI pain worst scores (p = 0.003), the mean BPI pain least (p = 0.08), the mean BPI pain now (0.06) and the mean BPI on average score (p = 0.03).

3.3.7.5 Adherence to medication

There was a difference in adherence rates between the two approaches, in that analgesics were taken on 99.8% of days in the 2-step approach compared to 89.7% of days in the 3-step approach (Table 32). This difference was not statistically significant however.

Table 32: % adherence to medication in the 2-step vs. 3-step approach

% Adherence to medication (SD)					
3-step	**2-step**	**Difference**	**Adjusted* difference**	**Adjusted 95% CI**	**Adjusted p value**
89.7 (25.0)	99.8 (0.01)	10.1	8.2	-4.7 to 21.3	0.21

**adjusted for baseline pain score and centre*

3.3.7.6 Use of escape medication

The use of escape medication also varied between the approaches, with the crude difference showing a greater use of escape medication in the 2-step approach. However, when this difference was adjusted for baseline pain score and centre, there was a lesser use of escape medication in the 2-step approach. The confidence intervals were wide and consistent with no difference between the approaches (Table 33).

Table 33: Use of escape medication in the 2-step vs. the 3-step approach

Use of escape medication† (SD)					
3-step	**2-step**	**Difference**	**Adjusted* difference**	**Adjusted 95% CI**	**Adjusted p value**
0.43 (0.51)	0.54 (0.53)	0.11	-0.03	-0.34 to 0.3	0.85

** adjusted for baseline pain score and centre*

† use of escape medication calculated by number of doses used divided by number of days data provided

3.3.8 Effect of adherence on the primary outcome measure

In light of the higher adherence in the 2-step approach, the primary analyses were repeated, with adherence added as an additional covariant in the model. This allowed us to examine the effect of treatment on the percentage of time spent in controlled pain in the first 28 days or the odds of having controlled pain on any given day, independent of adherence. The 2-step approach resulted in mean difference of 17.6 percentage points (95% CI –4.4 to 39.6; p = 0.11) a result similar to that obtained before adjusting for adherence. The odds of having controlled pain on any given day after adjusting for adherence were 2.74 (95% CI 0.7 to 11.3; p = 0.16) again similar to the results obtained previously.

3.3.9 Adverse Events

Overall the adverse event rate was low, so descriptive statistics only are shown below (Table 34).

Table 34: Adverse events in both approaches

	2-step approach (n = 19)		3-step approach (n = 19)	
	Mean (SD)	Range	Mean (SD)	Range
Total adverse events	2.5 (2.4)	0 – 9	2.1 (2.3)	0 - 9
Severe adverse events	0.9 (1.0)	0 - 3	0.4 (0.6)	0 - 2
Severe adverse events related to study drugs	0.3 (0.8)	0 - 3	0.05 (0.23)	0 - 1

3.3.10 Estimates of required sample sizes for definitive trial comparing a novel 2-step vs. the traditional 3-step approach

Using the standard deviations of the proportion of time spent with a pain score of ≤ 4 in both arms of the pilot study, we have estimated the sample sizes required for a definitive study, using a minimum clinically important difference of 10% and a maximum likely difference of 25%. Two calculations have been conducted in order to define sample size for studies with 80% and 90% power to detect a difference (Table 35).

Table 35: Sample sizes required for a definitive study with both 80% and 90% power to detect differences of 10 – 25% between intervention and control groups

Outcome measure	Clinically important difference	Power	α	Required sample size in each arm
Mean % of days with a pain score of ≤ 4 (SD)	Minimum 10%	80%	0.05	186
		90%	0.05	249
	Intermediate 15%	80%	0.05	83
		90%	0.05	111
	Maximum 25%	80%	0.05	30
		90%	0.05	40

3.4 A qualitative study to explore the views of patients considering morphine for relief of pain caused by cancer

The following chapter describes the results from the qualitative component of the 2-step trial. The characteristics of those interviewed will be described, including information about their primary cancer and its changing status at the time of recruitment, whether or not they had had previous contact with palliative care teams and the type of analgesic used at the time of the interview. The patients' own descriptions of the nature and impact of pain on their lives will follow, so that the description of the emergent themes can be read in the context of their pain experiences. The conformity of the interviews will be discussed as well as the way in which deviant case analysis validated the themes. Finally, the observed relationship between these themes will be explained and a model of the use of morphine and other Step III opioids in cancer pain proposed, informed by data gathered during both the 2-step trial and the interviews.

3.4.1 Characteristics of the participants

The eighteen participants ranged in age from 55 to 82 years. Nine were women. All of the participants lived with another person, usually a spouse, except one of the women who lived alone. Of the nine male participants, seven had advanced cancer of the prostate, one had cancer of the lung and one a cholangiocarcinoma. Four of the women had cancer of the breast, two had lung cancer, one a rare form of sarcoma and one cancer of the ovary. All of the participants had metastatic

disease. At the time of entry to the 2-step trial, three participants had received visits from a community palliative care nurse, but the others had not been introduced to palliative care teams. This was because they had previously been receiving life-prolonging treatment and so had not been thought to have required palliative care. Generally, their entry to the study was associated with either new evidence of disease progression, a new complication related to their cancer or the cessation of chemotherapy. These circumstances are significant in a patient's life, and often lead to a change in the focus of treatment from life-prolonging treatment to palliative care.

The pseudonym, sex and age and analgesics at time of interview for each of the participants are detailed in Table 36.

At the start of the interviews, all of the participants were asked to tell me about their pain, which was difficult for two of them. One could not because the interview was rushed since she very nervous about missing an oncology appointment. The other respondent had experienced a resolution of her pain since a change in chemotherapy and so did not have any pain at the time of the interview. The remaining 16 participants described how they had been struggling with pain and the pain experience, similar in all, seemed to be unrelated to the nature or cause of the pain.

Table 36: Characteristics of participants recruited to the interview study

Pseudonym	Age	Diagnosis	Analgesics at time of interview
Entered 2-step trial			
Rupert	63	Ca prostate	Regular cocodamol plus "as required" morphine
Patricia	68	Ca breast	Oxycodone
Andrew	80	Ca prostate	Oxycodone
Betty	69	Sarcoma	Oxycodone
Jim	82	Ca prostate	Regular modified-release morphine
Mary	58	Ca breast	Paracetamol
Vanessa	62	Ca breast	Paracetamol plus "as required" morphine
Tom	67	Ca prostate	Oxycodone
Karen	55	Ca breast	Oxycodone
Andy	57	Ca prostate	Regular modified-release morphine
Daisy	77	Ca lung	Paracetamol plus "as required" morphine
Gloria	66	Ca breast	Cocodamol
Did not enter 2-step trial			
Harvey	58	Ca prostate	Regular normal-release morphine
Ruth	62	Ca lung	Regular co-codamol plus "as required" morphine
Henry	69	Ca prostate	Cocodamol
Joseph	69	Ca prostate	Ibuprofen "as required"
Philip	68	Cholangiocarcinoma	Morphine "as required"
Margaret	68	Ca ovary	Nil

3.4.2 The impact of pain on the lives of the participants

Pain resulted in reduced mobility (7/18 respondents) and functioning (11/18), at times causing the respondents to give up their jobs (2/18), driving (2/18) or other activities (6/18). When describing how the pain had limited his walking ability, Andrew said:

> I think the worst bit of it was when um … when we went into Bristol to do some shopping, and I had to walk about 300 yards to the shops because I was out buying a new jacket, and I hadn't experienced pain like that for a long time. It was um – it took about quarter of an hour to get to the shop, I could only walk about 10 yards at a time.

Ruth described how the limitation to her mobility was affecting her efforts to recuperate following chemotherapy.

> Well it's very demoralising….Because, you know, I find um I have to lie down or um – and then I get it when I'm walking…and it comes on – sometimes it comes on when I'm walking, so I can't walk….So it's – yeah and that annoys me when I want to be fit, you know….So I find it's difficult in-between not overdoing it, and doing it.

Mary describes a feature that was common to many of the participants, which was that the pain could affect all areas of life, simply by "slowing" her.

> Um I'm a lot slower than I was… I mean obviously I don't – I mean I used to rush around here, there and everywhere, but now I've slowed down…I think before I do things…I don't do a lot of things that I used to do.

Pain also led to difficulty sleeping (5/18) and a feeling of being out of control (2/18). One respondent described "unbearable" intermittent pain that made breathing difficult. Jim described how when he was in pain, he could not concentrate and how this resolved when he had used his painkillers and they had relieved the pain. Eight of the sixteen respondents described themselves as being depressed, miserable or low in mood as a result of their pain. Patricia seemed to believe that this change in mood affected her ability to "fight" the cancer when she said:

> And I think finally, um at the point where I met with you, I had then started to feel very low, very depressed, and I felt that I was losing the fight because I could not – all of a sudden the pain, I think, had finally got to me.

Four of the respondents described the impact of suffering pain on their family life and how their families, observing them in pain, treated them differently. Harvey and Tom talked about the impact of uncontrolled pain on their wives and Gloria described how the pain affected her relationship with her husband.

> Yes it does affect my moods, yes. If it does come in the daytime, which it was before I was taking a lot of tablets, yes I was very nasty sometimes to my poor husband – he'll tell you.

Three participants talked about being unable to spend time with their grandchildren because of pain, including Patricia who said:

> When my grandson was here, or if I was going to them, I couldn't nurse him or play the usual things. Because the sternum, my sternum, the agony would last for something like two days.

Perhaps because of the physical and social impact that the pain had wrought on these people's lives, they described it as a difficult symptom to deal with emotionally. Patricia talked about the pain being her biggest challenge, secondary even to dealing with either chemotherapy or her mastectomy. Jim told how he felt that he was being singled out to suffer and when experiencing pain would question why.

It seemed that both the physical, emotional and social consequences of pain could be construed as loss for the participants. For some, reduced mobility or inability to drive resulted in a loss of independence. For some, their roles were threatened when they became unable to do household chores or other activities such as gardening. Others experienced a loss of self when treated differently by their families when they were in pain. Patricia seemed to sum up these losses when she said:

> But I just feel I've been robbed.

3.4.3 Emergent themes

After analysis of all the interviews, the themes from the transcripts were identified within four major analytical categories. These were:

- Anticipation of death
- Morphine as a last resort
- Role of the professional
- "I haven't got any choice" but to use morphine

The subsequent part of this chapter will describe the themes within these categories and illustrate their meaning using the participants' own words.

3.4.4 "You've got cancer, you're going to die": Anticipation of death

One of the most striking themes to arise from the interviews was the extent to which the development or presence of pain related to cancer caused the participants to consider the extent of their disease. Contemplation of anticipated death then followed. This may have been in part explained by the frequent response of the oncologists when new pain was reported, which was to request further investigations to look for evidence of disease spread. For some, the original diagnosis of cancer or the news of its recurrence had been the result of investigations for pain, strengthening the association between pain and severity of disease. The anticipation of death also seemed to be aggravated by news of more extensive disease, or the change in goals of care (from life-prolonging treatments to a focus on quality and comfort) that many of the participants had experienced in the weeks preceding study entry.

For some, the presence of pain made them question whether or not their disease was more widespread than their doctors were aware. A few participants actually distrusted information they had been given by their oncologist about the extent of their disease. Mary was a bit hesitant to reveal this, as demonstrated by the pauses during the relevant part of the conversation.

INTERVIEWER: And so as the pain has become a feature of the cancer, and as it has got worse, what are your thoughts then, what are you thinking then?

MARY: I think that obviously the um cancer has got worse than it was.... But um they tell me no, but (pause)

INTERVIEWER: Go on.

MARY: What they tell you and what actually is happening is – can be sometimes two different things. I mean I think they tell you what you want to know.

Not only the presence of pain, but also the need to take analgesics made several participants anxious that their anticipated death would be hastened. Tom clearly highlighted this fear when he said:

Um I'd had a hard job to accept I'm going to die.... It's not easy for me...um because I still – I feel that there is something somewhere, you know, people do beat it, and I feel I can. But the more the painkillers have

to be increased, the kind of more it drags you down a bit, and you can see that the future is going to be harder, and you have to fight that much more.

Generally the psychological impact of unrelieved or worsening pain was negative, because of its association with disease progression and death. As Mary said:

> The pain is niggling, and then it keeps reminding me, "You've got cancer, you're going to die."

3.4.5 "Surely I can't be that bad?": Morphine as a last resort

The overwhelming concern that the participants had about morphine was that it was a drug that was used when a person with cancer was thought to be imminently dying. The word used most commonly by the participants to describe this was "last"; either last resort (used most frequently), last minute, last stage (of the cancer), last ditch or last step. Because of this, some of the participants commented that they had been frightened at the first consultation when a drug described as being similar to morphine was considered a possibility for their pain. Margaret described her initial emotion as being one of fear when morphine was mentioned.

> Um well it did, in that it made me fearful. Because um I, rightly or wrongly, always associate morphine with the sort of top end of the scale of intervention, meaning the sort of the last resort almost.

Betty described a similar reaction and also made the link between cancer and death.

> Quite a reaction actually, because I've always um associated it with people really ill with cancer, and near the end of their life.

Mary described how she saw morphine and death being linked.

> So morphine and pain and death, it's all in one to me.

Vanessa spoke of how she thought that using morphine would mean that she was dying.

> No, but when you get to morphine you think the end is nigh, you know?

Because morphine was seen by all the participants as a drug that was used when someone with cancer was thought to be dying, several said they considered using morphine meant that they were accepting that they were dying. Patricia described how she could not accept she was ill enough to need morphine.

> I'm not ready to take on the next step of the path of my, of the path of my life. You know, um I – I very much sometimes look at myself when I've got no pain, and I know that I look fine, and think they've got it wrong.

Ruth also could not accept that she was ill enough to require morphine and when trying to explain why she was reluctant to use extra doses said:

Surely I can't be that bad?

Three participants had refused the drug when it had been offered initially, as a means of trying to postpone death. Mary described her conversation with her oncologist when initially offered morphine.

> Well I said to him [her oncologist] then, "I won't take it." And he said, "Why?" And I said, "Because I've got a thing about morphine." And then he said, "Why?" And I said, "Because I think it's the last – the last stage of the cancer. When you have morphine."

Ruth tried to explain why she was reluctant to use "as required" doses of morphine, even though she had found it useful for her pain.

> Um no I – I think – I think I've more or less accepted now that it's. I think it's more to do with the fact that if I take quite a lot of this morphine then I – it just means I'm getting worse. And I don't want to get worse. Well I mean I know I'm going to get worse (laughs) but um it's a sort of puritanical thing you know.

Gloria also spoke of morphine meaning progression of disease and death, because of her perception that the aim of treatment had altered to providing symptom relief but not modifying the cancer.

But as soon as I have to take morphine, I know it's coming closer to not being treatable, because all you want to do is just stop the pain, not treat the problem.

She went on to confirm that using morphine would mean she had accepted her death as inevitable.

GLORIA I'm 67 but I'm too young, I've got another – give me another ten years and I'll take the morphine if you like (laughs)

INTERVIEWER: (laughs) Right. And if you were to use the morphine, would you feel you were then accepting that you might be dying?

GLORIA: The inevitable yes.

Those who had commenced morphine worried that others would interpret this as bad news. Mary had not been able to tell her children.

But I did worry that um my children – certainly my daughter, my eldest daughter – might think if I'm on morphine that I am worse than I actually am….Because that, to us, was the last minute drug.

Ruth also spoke of her anxiety at informing her daughter that she had needed to use morphine because of the message she thought it might convey.

It's like everything else has failed.

This final quote from Philip about the perception of morphine sums up what the other participants were saying. Morphine is seen to represent a terminal prognosis by patients and their families. It seemed as if the commencement of morphine represented a symbol for the commencement of the dying process.

> Yeah it does have this sort of reputation with morphine – oh it's almost sort of an explanation as to how bad things are. That if someone says they're on morphine you sort of – as a lay person – almost understand that he's not near the end, but he's not far away. And it's almost a painkiller which is used because it doesn't matter. It's going to clear the pain up, but you're sort of not going to be here in a year's time so if you get addicted it doesn't matter. It's there to give them a peaceful end.

One of the participants, Andy, did not discuss associating morphine with death at all during the interview. However, once the microphone was switched off his wife mentioned that when she had gone to collect his first ever prescription of morphine, the pharmacist had personally handed her the tablets (which was not their normal practice) greeting her with the words "is he worse then?" During the subsequent discussion off-tape, Andy said that he had been very anxious when first offered morphine because he, like other participants, associated it with dying. This was difficult for him to articulate and he began to cry. He said the following words, which he was happy for me to quote:

> The three words that strike the fear of God into your average working class bloke are 'morphine', 'palliative' and 'hospice'.

The association of morphine as a last resort was either informed or strengthened by the perceptions of both its side effects and the manner in which it is used. Whilst a knowledge of side effects came from some people's personal experience, the majority of the participants' knowledge came from hearing stories about or witnessing others, usually relatives or friends, who had taken morphine.

3.4.5.1 "The morphine trail": Morphine in increasing doses

Many of the participants described the way in which they considered morphine was given to people with cancer who were thought to be dying. They described increasing doses being given, not because of lack of effect, but as an inevitable consequence of having commenced morphine. Harvey called this "the morphine trail" and anticipated that he would require increasing doses when he said:

> And so I reckon I'm on the morphine trail and I'll just have to keep on increasing the dose.

Karen also felt that dose increments were inevitable.

> Well I know they said it was a low form of morphine, but you always hear that when people are really in pain you give them morphine. Obviously I believe that morphine is probably the strongest painkiller, and obviously all they can do is keep piling the dose up.

Some developed this further; implying that morphine became the cause of death in patients because of the unavoidable dose increments. Jane had memories of her father's death.

> Well she [the research nurse] said I made a face. And I said, "Well it's because I associate it with death basically." I remember my father who was on more and more morphine until he died.

Betty also had memories of the use of morphine when her close relatives were dying.

> And um a bad experience that my father died of cancer, and father-in-law, and neighbour, and I used to see them having more and more, upping their dosage of morphine.... And come the end they just had it injected into them.

Whilst recalling her memories of this time, she seemed to feel that her father-in-law had deteriorated quickly once he had commenced morphine, and when asked if she thought the morphine had caused his death, she agreed, as demonstrated in the following text.

BETTY: Oh yeah, oh gosh yeah, yeah. Because um when he went in he didn't seem too bad actually when he was taken in, but within a few days

INTERVIEWER: he'd died?

BETTY: he'd died yeah.

INTERVIEWER: Right, and am I right that part of you felt that that was because of his morphine being increased?

BETTY: Yeah, but then when you look at it there is so much pain anyway, nothing else could be done for them, and they were both in their eighties.

Betty was not alone. However, those who discussed the use of morphine in increasing doses and its apparent hastening of death did not appear to judge it negatively or deem it unethical. Instead they described a tension between life and freedom from pain, and that the freedom from pain therefore justified the perceived shortening of life, as when Joseph states:

> It's a fine line, isn't it?

It was interesting that it was also Joseph who was the only participant to associate morphine with malicious illegal killing. Although he discussed the tension between freedom from pain and pain relief when morphine was used at the end of life, he seemed to be talking about a different practice altogether when he said:

> Yes um I suppose it's only because um you have the feeling, and I don't really know why, but um you have the feeling it's er not a very nice drug, it's often used if someone is in er severe pain, or terminal, or something like that. ... Um somewhere in the back of my mind I tend to feel that doctors don't know what the correct dose of morphine is anyway. Er I may be wrong about that, but I have, in the back of my mind I have that feeling – and they just go on giving it, shall we say. ... But if someone's terminal,

> well you do of course hear of occasions when it's used um – what shall we say? – when um – in crime, in crime, shall we say. … Morphine is used to dispose of someone. (laughs) Um you do hear about that.

The perception that morphine is given in life-threatening doses seemed to further reinforce the belief that morphine was used only when someone was dying. It was as if the price to be paid for pain relief from morphine was so high, it would only be worth considering if death was likely to be soon, as the following words from Philip show:

> My association is that you're getting near the end when you're on morphine, and therefore you want a painkiller which is going to knock out the pain, you're not really bothered about anything else, you just want to actually get rid of the pain. And if they go a bit gaga well what can you expect, it's either-or. Either-or, you know, you're either not bad enough or you are bad enough, if you see what I mean.

3.4.5.2 "Seeing them dying": Origins of the associations

For most (11) of these participants, their associations with morphine were linked to previous experiences with relatives, usually older family members, at the time of their deaths. When asked where his associations with morphine came from, Tom said:

> All the information that I've got in my head has come from watching them, hearing about them and seeing them dying.

Participants carried memories, often from many years previously, of conversations with professionals about increasing doses of morphine or of seeing loved ones hallucinating or confused as a consequence of morphine. Vanessa remembered witnessing her grandmother hallucinate with morphine when she was a small child.

> Um it's strange how things stick in your mind, because I was only just four I think. And I went upstairs, and she [her grandmother] said, "There's a lady under the big floor." And I've never forgotten that. And I came down and told my mother and my aunt, and they said, "She's delirious, it's the morphine."

Some like Ruth were even told by professionals that morphine, although being used as a comfort measure, was perhaps hastening death.

> No – well except of course it puts people out of their misery, I mean I was only too thankful. In fact when my father was dying we were asked if they could increase the dose although it probably would kill him. And we said yes. I mean we didn't want to put him through … he was dying, and so we said yes, and of course they did. So for him I was only too thankful.

One of the participants described how, 30 years previously, she had been given some morphine tablets for her father who had been dying of cancer. He had suffered uncontrolled pain as a consequence of his cancer, but was only given

morphine in his final hours. The tablets had been left for her to administer because she was a nursing student. Her father had died two hours after the first tablet had been given, leaving her with the belief that she had "just finished him off". This experience was reinforced by practice that she witnessed as a nursing auxiliary in elderly care wards in hospitals, where syringe drivers containing morphine would be commenced routinely when someone was thought to be dying.

Others mentioned conversations with friends and families or hearsay as the source of their associations. Mary remembered a conversation with the husband of her friend who had died recently, suggesting that her death would be soon because morphine had been commenced.

> No, they only went on morphine – I mean my friend that died of a brain tumour, her husband phoned up and said, "Oh she's being injected with morphine now, if you want to come and see her you'd better come and see her".

Some also described the media as displaying negative images of morphine as a consequence of reporting news of drug addiction or reinforcing ideas of morphine as an end-of-life drug in fiction. Joseph could not remember any personal experience of seeing morphine used and could only cite the media (newspapers, television and radio) as sources of information when he said:

> No I think it's only what's built up through the years, possibly through the media, I would have thought.

3.4.5.3 Other associations with morphine

Six of the participants with previous experience of opioids mentioned side effects as an association. Mary remembered previous painkillers causing constipation and making her feel more unwell than she did already. When asked if she felt comfortable using painkillers regularly she said that she had to use them in order to be able to get on with her life but that she didn't like taking painkillers. When asked to explain this she replied:

> Well I just – basically I just don't like taking tablets. I mean I just don't um – I am a bit scared of taking new tablets, messing up my stomach like, you know, making me constipated, making me ill, bad.

Vanessa, who had witnessed her grandmother hallucinate with morphine had herself experienced hallucinations with morphine. When describing how morphine brought all her fears to the surface, which seemed to be its psychological impact on her, she immediately went on to explain her hallucinations, which she described as a "bad effect".

> INTERVIEWER: I was wondering if the morphine being offered as the treatment, to some extent reinforces what the pain makes you feel?
>
> RESPONDENT: Um frightened, yeah it does, yeah…it brings all my fears to the surface….Yeah and also it actually has the bad effect on me that I hallucinate quite easily….In the day um particularly, I can't explain it terribly well, but if I take it during the day, you know, it's a low dose sort of thing, I will doze, but it's not an ordinary doze, I sort of see faces and things.

Rupert spoke of his previous experiences of drowsiness and hallucinations when he had used morphine several months earlier for his pain caused by his cancer. During the trial remained extremely reluctant to consider either "as required" morphine or regular modified-release morphine. This was in spite of recording high daily pain scores and experiencing marked loss of function and social activity because of pain.

Some of the participants associated morphine with unavoidable sedation. Gloria considered it to be deliberate sedation, again without a negative judgement of this practice. The intended "slowing" seemed to be considered an act of kindness as demonstrated by the following quote, where she says the intent is to "relax you":

GLORIA: I should imagine they want to slow you down, isn't it, and make you tired?

INTERVIEWER: Are you saying that's a side effect, or are you saying that's almost a deliberate effect?

GLORIA: I think it's a bit of both.

INTERVIEWER: OK tell me a bit more about that?

GLORIA: Well because I've – I've sort of seen it. And um as soon as you have the morphine – and I also saw my young nephew as well I forgot him – as soon as they have the morphine then they're just sleeping all the time.

INTERVIEWER: Right, but you think some of that is intentional?

GLORIA: I – I – well I don't know, I can't say I do – I don't know.

INTERVIEWER: You don't know.

GLORIA: No.

INTERVIEWER: But there's a slight reservation?

GLORIA: There's a slight reservation thinking that's what it's to do, to slow you down, to relax you.

Again, there was a sense that these side effects were considered inevitable, the price that must be paid for pain relief. Gloria, who was trying to remain active in order to be able to look after her sick husband, described what she would have thought was ahead had she been randomised to oxycodone:

INTERVIEWER: So if we had given you morphine, or something like it, would you have?

GLORIA: I'd immediately have thought, "That's it, I've got to slow down and I can't do all what I want to do."

When asked what she would have done if she had been randomised to oxycodone, she said that she probably would not have taken it.

Nine of the participants talked about addiction. Those who had a previous smoking habit themselves, or had witnessed their spouse's smoking habit found it easier to describe what they meant by addiction, usually in terms of "needing to keep taking morphine". Joseph's wife was currently trying to stop smoking and when asked what being addicted might mean he replied:

I would imagine it meant that you, you know, you really had to use it, you had to keep on taking it, you know, you felt you had to keep on taking it …

> um even perhaps if the pain wasn't that bad, perhaps you would feel that um, "Well I'd better have some more," I would think.

He did then also comment that addiction might mean being "slowed down" and being "not too well". Joseph had mentioned addiction because when he had first been prescribed morphine for pain caused by a bone metastasis his surgeon seemed worried about it:

> And um I don't think he [the surgeon] was too keen on giving it to me, to be honest with you, because to begin with I um was taking three 50 ml, I believe, three teaspoons anyway, and he asked me to cut it down to one as quickly as I could.... And then he said he wouldn't like to see me on it for too long. And then I was taken off of it altogether, and I think, by then, I'd had some radiotherapy and some hormone treatment. Um he – he – I think he thought I – he might get a reaction from me when he suggested I used it. Because um he said, "It's alright, you won't become addicted to it." So he must have thought that most patients thought you could get addicted to it – which I believe is correct, of course. But um I wasn't thinking that.

For others addiction to morphine was more difficult to define and sometimes seemed to be confused with being given higher and higher doses. Betty raised addiction and drug addicts early in the interview. When asked if she had been anxious about becoming addicted, she seemed unable to say clearly what it might mean, but perhaps using more and more and therefore feeling weaker and weaker with shortened life as a consequence:

More and more and … that would be the end of your life, yeah.

Andy was asked how he would imagine he might behave if he was addicted to morphine and replied that he would see it as a downward spiral. When asked to clarify he said:

Well there's sort of no getting out, once you've started on morphine and become addicted to it, it would be a hell of a job to get out of trouble and stop taking it – if that makes sense to you.

When Tom mentioned addiction as an association of morphine, it was not seen to be a practical problem since he considered any remaining life would be short.

Um not so much the addiction.... Because I think I had accepted that if I cannot beat this then the addiction um might be there, and it isn't going to matter if the road I'm on is one that's going to end, you know, relatively shortly.

Harvey mentioned tolerance because he had read about it in the patient information leaflet.

"Well I've been told that they have to increase the dose. And I always read the leaflets that come with the packet.... But it says that you become tolerant to it and you'll have to increase the dose"

Henry, perhaps because of his role as a city councillor, made the distinction between illicit drugs and morphine during the interview, when he said

> No well I've heard nothing negative about morphine. Now if they asked me to take cocaine or heroin or something, well then I would have been concerned. … But I haven't heard anything er untoward about morphine.

Margaret did not think addiction to painkillers was the same thing as addiction to illicit drugs:

> Yes I think that um one can become addicted, if only if you're using them as a crutch, tablets. I mean you can talk about paracetamol, you see people who pop pills, paracetamol, aspirin or whatever, just um – and they can't do without them for some reason. It's the act of taking the pill, like smoking a cigarette, sometimes it's not so much that the pill is going to do them much more good, I think one becomes psychologically addicted, not necessarily dependent like if, you know, like someone had cocaine, you know, and becomes an addict, it's not the same thing.

3.4.6 Role of the professional

The role of the professional in pain management was referred to in some way by most of the participants. They referred frequently to three main areas: communication about pain, communication about opioids (especially the way in which they were offered to the participants) and trust in the professional.

3.4.6.1 Communication with the professional

The manner in which consultations were conducted following reports of pain was important. The participants expressed a need to have their pain believed even if no obvious cause was found and the need for pain to be considered an important topic during the consultation. Patricia described how it had been a relief to have the research nurse sit down and listen to the story of her pain and resolve to do something about it. She felt that previously she had simply been offered various analgesics without explanation and that her pain had not been dealt with because no cause could be found. It was distressing to hear her say that she had been made to feel her pain was not real, as she does in the following words, describing the management of her pain at the oncology centre.

> Because they [the oncology team] are just mystified. They don't know what I'm saying, they don't understand my pain at all. And therefore it's made me feel that I'm not – that I'm lying...that makes me feel that I have been making a fuss about nothing. And I haven't made a fuss about nothing, I'm not like that.

Andy, who had multiple bone metastases from his advanced prostate carcinoma also described similar experiences and he too noted the different reaction he perceived when he saw the "pain team" (palliative care team):

> Um yes I think the er – the pain team, they basically knew what I was telling them was the genuine article.... Sometimes you go to the doctor and say, "Well I'm getting this pain," and they don't always necessarily tend to

> believe you.... And the pain for me is real in my left – right knee, whether or not I'm imagining it, which I'm sure I'm not, but er it doesn't make any sense why I've got the pain.

Participants also spoke of the need for the professional to be both confident and competent when discussing the use of opioids. Philip and his wife described the way the palliative care nurse dealt with his pain as being "wonderful". When asked to explain why, they spoke of her attitude to them when treating them as equals, her confidence in painkillers and her knowledge, as shown in the following exchange.

> INTERVIEWER: And how was she [the palliative care nurse] when she was discussing that?
>
> PHILIP: Oh she was very relaxed. It was obviously her field, I mean she was obviously well genned up on it, and she was talking to us both about it. It was, you know, as far as she was concerned I think it was a matter of that's what she's there for.

This was different to the attitudes and knowledge of other professionals they had encountered dealing with his pain.

Since some of the participants had commenced a Step III opioid by the time of the interviews, it was possible to explore what words used during the consultation had helped them to accept the prescription. Vanessa, amongst others, said that it had been useful to hear that they would be using a low dose of opioids and went on to

describe how an oncology nurse had persuaded her to use some morphine for the pain in her leg, which was later found to be due to a pathological fracture of her femur.

> INTERVIEWER: And what was it about the way she [the oncology nurse] said that to you?
>
> VANESSA: Well just that she said, "You are being silly. Dr. Thomas has told you that morphine is not dangerous in that sense, and it's a very mild dose, and people take it for all sorts of things, not just cancer."

Karen also noted that the language used when describing the trial drugs helped with her decision to enter:

> Um probably – because it was only a low dose I'm probably quite happy to take it. But I think if you would have told me, "We're putting you on this drug and there's quite a high dose of morphine in it," I probably wouldn't have done it, I wouldn't have took it.

When recruiting to the trial, we had been careful to inform potential participants that they could leave the trial, or stop trial drugs at any time, without it affecting their care, according to Good Clinical Practice guidelines. Betty was one of two interview participants who said they had found it reassuring to hear that if necessary, because of side effects or other reasons, the opioid could be discontinued and that this made the decision to commence the opioids easier.

No, no I thought yeah I'd give it a try.... And like um Dr. Sarah said that you can come off it, I didn't have to um stay on the trial if I wasn't happy with it.... So I thought yes give it a try, and it seems to be working fine.

3.4.6.2 "It's your choice": Opioids offered as a choice

Another way in which the language used by the professional influenced the use of opioids was in the offering of Step III opioids as a choice for the individual. Harvey mentioned the fact that when the morphine was offered to him by nursing staff in response to his reporting of pain in a hospital ward, he was told that it was his choice to use it or not.

They actually don't say, "Mr. Smith, would you like to take the morphine?" They always say, "It's your choice."

He found this difficult, particularly as he had come to believe that he did not have a choice. If he wanted to be out of pain, he needed to use the morphine:

INTERVIEWER: "And in relation to being offered morphine, and being told morphine is your choice, what do you think about being offered morphine as a choice rather than being...?"

HARVEY: "Well I realise now that it isn't, I haven't got any choice."

The fact that he realised that morphine was necessary for pain control and yet offered as a choice, increased his suspicion of opioids and he said:

If it is my choice, what are they not telling me?

Four of the respondents mentioned that when opioids were offered as a choice, then they did not use them. When later that choice was removed, they took them. In the following text, Karen describes how during the randomisation process, the opioids were "chosen for her" and this allowed her to use them.

INTERVIEWER: Right, do you think it's better to have it offered as just, "This is the option"?

KAREN: Yes I think that's the best way to do it.

INTERVIEWER: Right, and why do you think that might be the best way?

KAREN: Um because the choice wasn't up to me.

INTERVIEWER: OK tell me more.

KAREN: Um well the choice was, in the end, you know, they offered it and said what I was going to have.... And I just – because I chose that envelope, or that envelope was chosen for me, and because you said it was a low dose, I decided to go for it.... But if I was asked to say go onto morphine or something else, I probably – because of what I said at the beginning, I probably would have took the other option.

3.4.6.3 "Advised to take it by the medical service": Trust in the professional

It was clear that trust in a professional was also an important factor when considering whether or not to commence the opioid they offered. This was mentioned by eight of the participants. Harvey, who had said how mistrustful he was of professionals who offered him morphine as a choice, was eventually

persuaded to use it by a night-nurse during an admission to a urology ward. When asked why this particular nurse had convinced him to try using morphine, he said:

> Well she was just a human being, you know….And you realised she had great experience…. You know, and she was just er – I mean I knew she was a very smart person, and that she knew what she was doing in everything she said…and you can't say that you know how to build a wall, or you know how to do this, or you know how to do that, but you get to know by looking, by watching and by listening, you get to know the person who is good at their job.

Patricia commenced oxycodone within the 2-step trial having felt "listened to" and that the research nurse believed her pain. During the interview she mentioned that the first doctor who prescribed her morphine, which she did not use, was a general practitioner she did not know well:

> Yes definitely it made me feel, "Oh morphine, well this is something people take, you know, when things are really getting much more advanced and bad. And, you know, where am I?" You know, um and er I didn't have, at that time, any intention of taking it…. Because I felt that at the time he was a reasonably – although he'd been in the practice a long time, he was a reasonably new doctor to me.

The importance of trust in the professional varied in degree. The two examples above show how trust or confidence in the professional allowed the individuals to

make their own decision to commence opioids. Those, such as Jim, who seemed to describe strong faith in health professionals, appears to have abdicated the responsibility for decision-making to the professional; Jim says:

> No, no I'd think to myself, "Well they're putting me onto something else which is a stronger drug to help me."... And I just accepted that. I mean when I go to any doctor – well most doctors anyway – um ... I always go in there with the idea that um they know what they're doing.

This trust allowed him to accept morphine, even though he had had negative information about morphine from other sources, as shown when he said:

> I mean over the years I've heard about it with all sorts of things. But um it didn't worry me because I was being advised to take it by the medical service.

3.4.7 "I haven't got any choice" but to use morphine: factors influencing the decision to commence an opioid

The majority of the participants had been prepared to enter the 2-step trial and so accept the possibility of randomisation to a Step III opioid. However, at least one of the 2-step trial participants said she would not have taken the oxycontin had she been randomised to the experimental arm. Eight of the participants had already commenced a regular opioid for moderate to severe pain by the time of the interview but we also witnessed several participants either resist our attempts to commence them on regular morphine during the trial or decide not to use extra

doses of "as required" morphine when experiencing poor pain control. This gave us an opportunity to explore the factors influencing the decision to commence opioids within the interviews. Some of the participants had been offered morphine previously and made references to these episodes, allowing us to gain more information about their decision-making. The role of the professional in this decision has been highlighted already. Other factors which seemed to influence the decision to commence regular opioids or indeed to take doses of "as required" medication included:

- concern about the effect of unrelieved pain on others
- the severity of the pain

3.4.7.1 Concern for others

Those participants who described a lot of contact with their family, particularly with extended family such as grandchildren, were aware that others were distressed by witnessing their pain and some of their decisions were influenced by the wish to avoid this. Andy was very closely involved in the lives of his family all of whom lived nearby and he and his wife provided childcare for many of their grandchildren. He had initially felt very strongly that commencing Step III opioids was a negative step and was desperate to avoid using them, but in the following words described how his role in his family meant he took extra doses to relieve his pain.

> I had to do something, although everything in me was saying, "No, no, no…." But I realised I had to do it. I'm a father, I'm a granddad, I had to do something.

He also spoke of the way in which his pain had an impact on his wife and how this affected his decisions:

> But at the end of the day I know – you know, my wife is having to live here with me, and if I am in pain, or ache like that, she's suffering as well…. So I take it…. So some of this I am doing for my family.

Harvey also had noted the impact of his pain on his wife. He said that he had found the morphine to be beneficial for his pain, so accepted that he would need to keep using it in order that his wife did not need to witness his suffering, when he said:

> You see, because I've known what I'm like when the pains come back, life is so intolerable that I haven't got any choice, and I've had to find that out myself.

When asked about influences on his decisions about painkillers, Rupert also talked of how improvements in his pain control would have benefits for all of his family:

So anything I do has obviously got to relate to them. So if I can make my life better, and it reflects on how I am with them, fine, I'll go with anything that – I think will benefit all of us.

3.4.7.2 Severity of the pain

Most of the participants mentioned that pain would have to be, or had been, severe before they would contemplate using morphine or other Step III opioids.

I didn't really give it a thought. My main thought was for any sort of drug that would get rid of this bloody pain – I would have accepted anything. (laughs) (Andrew)

Um I think at that stage I was so desperate with the pain I would have done anything. (Vanessa)

I think the only difference is, then I was in severe pain and I was glad to get the pain relieved. (Joseph)

I suppose it's if you're in pain you'll take anything that will make the pain go away…To be honest I couldn't care less, if it stopped the pain. (Philip)

It was as if severe pain then gave them permission to take opioids, or perhaps severe pain meant the benefits would outweigh the potential harms. Some of the participants mentioned they did not know how severe their pain was in comparison to others. This was important because their decision to commence

Step III opioids was being based on pain severity rather than an understanding of the analgesic ladder or a step-wise approach to pain management. Some questioned how they would know if their pain had become severe enough to merit opioids, although the majority described that their pain would have to be extreme before they would consider them, as demonstrated when Gloria says:

> I would have if like...like I said, I'm not that silly that I would like to sit in dreadful pain. Because if there's something to help the pain, then I would take it. But I'd have to be in excruciating pain to take it regularly.

3.4.8 Dynamic associations

It seemed the anticipation of death that was such a prominent feature of these interviews was perhaps what resulted in the overwhelming impression of morphine being "a last resort". This may have been exacerbated by the recent progression of disease or change in goals of care that participants had experienced. It was clear that they interpreted being offered morphine as a signal that they were entering the final stage of their disease. Betty explained that there was a difference between her husband having morphine for kidney stones and her being offered morphine when she was told she had metastases from a sarcoma:

> BETTY: And then on the other hand, my husband suffers with kidney stones...and when he's been really ill the doctor has either given him morphine injections or pethidine...but when – when er they said I had tumours, and then morphine, you think, "Oh my goodness it's – you know.
>
> INTERVIEWER: Oh my goodness what?

BETTY: (laughs) It must be pretty bad and er..... you know you sort of have more and more morphine and er that puts the end of your life, sort of thing, doesn't it?

Some of the other respondents also mentioned that it was the presence of their cancer which meant they were frightened when offered morphine. When asked how it would feel if the next painkiller offered after paracetamol for cancer pain was morphine, Daisy answered "terrible", and went on to say:

I feel morphine – it means they put you on morphine, and you've got cancer, it means you're going to die.

The fear of morphine because of the presence of cancer was highlighted very clearly by Margaret, who discussed how she had felt very positive about having had a prophylactic oophorectomy some years previously, in order to prevent ovarian cancer. When given morphine post-operatively she was not concerned and certainly did not have the same reaction that she had experienced when being offered it after reacting badly to her first cycle of chemotherapy. Comparing her recent experience to that time she explained:

But when – you know, these last few months I know I have been seriously ill, very seriously ill, and I think that was a completely different situation in which um I knew that there was a possible end, that there was not um – it wasn't – it was more distressing. It was er – I felt there wasn't much future, and you feel you're just being um – you're just being made comfortable

> while you're still alive. Whereas before it was something to help me with the future, to prolong the future, so to speak.

It seemed then that it was certainly the presence of their cancers and possibly the recent changing disease status that meant morphine was being interpreted as an unspoken terminal prognosis and therefore shunned as a rite of passage towards an inevitable death. However, some of the participants had accepted Step III opioids and six of the eight who had commenced either regular morphine or oxycodone spoke of the confidence in these drugs they had developed since using them. Andy spoke of having felt "forced into a corner" before he eventually commenced morphine, but having done so said he had "improved his quality of life by 85%" and that he was more comfortable with using it.

> Basically yeah. I daresay there probably are other options but um I'm quite happy to take it now.

Two of the participants felt that they had more confidence about their pain control in the future. Daisy had not used regular morphine, but preferred to simply use "as required" oral morphine, but both she and her husband said:

> It's taken some of the hit and miss out of the future.

Tom had initially felt that any painkillers were taking him "down a path he didn't want to go down", but when asked if that had changed after commencing regular oxycodone within the trial he said:

I don't feel it's the last step.... With the oxys.... I think this could take me through all that I have to pass through into the future.

Patricia felt that she had been given back some control because her pain had been dealt with.

Um since the programme that I've been on with you, with the painkillers, it has turned my life around because it's freed me up from this terrible pain.

It also seemed that she no longer associated morphine with death:

INTERVIEWER: But your main association with it then would be that it's a drug at the next stage?

PATRICIA: Yes hmm, but I would say, for me, um that over the last fortnight my mind has changed dramatically (laughs).

3.4.9 Uniformity of responses (data saturation)

Whilst only 18 interviews were conducted because of the sampling strategy used and because of the frailty of the population being interviewed, no new themes arose after the first few interviews. Subsequent interviews were used to confirm and elucidate theories that had already arisen.

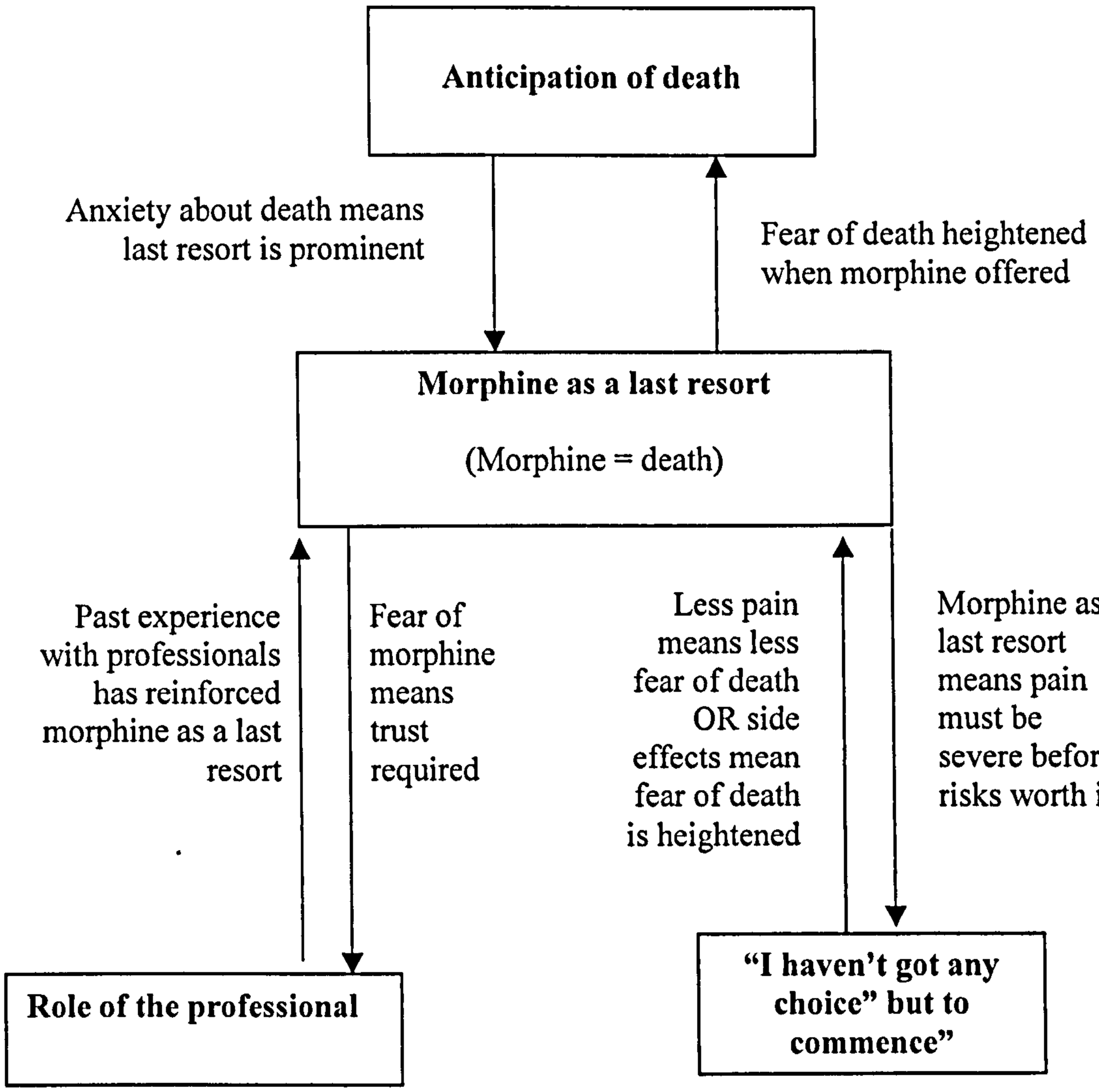
3.4.10 Deviant case analysis

Almost all of the participants discussed either their disease progression or lack of response to chemotherapy with an awareness of their mortality, although the word death or dying was not always used. Only four did not say during the interviews that they associated morphine with death. On careful re-reading of these four interviews, it seems likely this is because these participants had been unable to fully acknowledge or discuss their death with professionals, either during the interviews or during the 2-step trial. It is possible therefore that these participants also associated morphine with death, but their inability to talk to me about their own death meant that they could not raise the subject during the interview. This was best demonstrated by Andy who had been described by his oncologist as being unable to talk openly about his prognosis. He did not mention death when talking about morphine during the interview but when the tape was turned off and his wife started to describe the episode with the pharmacist when the first prescription for morphine was dispensed, he began to talk about how frightening it was to be offered morphine because everyone saw it as a death sentence. I think these negative cases reinforce the "morphine as a last resort" theme.

3.4.11 Relationship between the themes

What is prominent from the interviews is the way that these themes are clearly all interrelated, with each having the ability to influence the other. If morphine representing death because of it being a "last resort" is central to the interviews, then the other themes are influenced by or can influence this central theme in some way (Figure14).

Figure 14: The relationship between the themes



Central to the participants' experience is that cancer pain causes them to consider their anticipated death and causes them loss. This loss is either experienced as a physical symptom such as reduced walking ability or as a loss of role or self, for example when contact with family members is affected as a result of pain. It is likely that these losses then worsen the pain that is being experienced, because of the multi-dimensional nature of pain.

For most patients, talking about uncontrolled pain in a consultation will result in Step III opioids being offered when appropriate. These interviews show that this provokes fear by reinforcing the anticipation of dying. This occurs because if a

patient associates morphine with death and is then offered morphine, they are more likely to assume that their health professional thinks they are close to death. Those patients who associate morphine with being "slowed" will also anticipate a further reduction in their function. Thus, for the patient, the offer of morphine for pain relief apparently threatens to reinforce the emotional and physical consequences of the pain itself. This may explain why the patient often rejects the initial suggestion of morphine or another Step III opioid for cancer pain.

If, however, the consultation results in both the acceptance and use of Step III opioids then two scenarios are possible. If the opioid works and pain is better controlled, then the patient is no longer frequently reminded of their death. Improved function leads to more faith in Step III opioids as well as greater confidence for the future. This allows them to lose the association of morphine or other opioids as a "last resort", if only because they are still alive and possibly because they are more functionally able than they were before commencing morphine.

However, the second possible scenario is that the opioid is commenced but causes side effects. These side effects may cause increased loss of function due to the neuro-toxic side effects of sedation or hallucinations or by making the patient feel less well because of other unpleasant symptoms such as constipation (a side effect that was anticipated by Mary). This may then increase the association of Step III opioids with loss of function and/or dying. Strengthening of these negative associations by personal experience of side effects is likely to lead to future

refusal of Step III opioids, as demonstrated by Rupert during the trial, when his previous experience of side effects prevented him from attaining pain control.

So, for those patients who can no longer refuse morphine because of the severity of their pain or concern for others, a successful experience should allay their fears and dispel negative associations. However, a negative experience due to side effects is likely to prohibit either further dose increases or the use of "as required" doses for breakthrough pain or even lead to stopping the opioid. All of these result in uncontrolled pain.

This dynamic relationship reinforces the importance of the role of the professional managing pain caused by cancer. During the interviews the participants told me ways in which negative associations had been confirmed by professionals and how perceived ambivalence towards Step III opioids (when offering them as a choice to the patient) reinforced the negative associations. They also told me how certain language used by professionals helped them to accept a prescription for a Step III opioid and that it was useful if the professional spoke confidently and positively about morphine and other opioids. They were more likely to accept a Step III opioid if they trusted the health professional, a trust that was earned by listening to and believing stories of pain.

The overwhelming implication of these interviews is that we do not have to accept patients' fears or concerns about opioids as a reason for poor cancer pain control. This is particularly true if we consider that the professionals themselves appear to be a source of the negative associations. We have a better understanding now of

what these concerns are and we now need to consider how we address them, at both an individual and societal level. There are also implications for the way in which professionals offer morphine and monitor side effects. This will be dealt with in the discussion chapter of this dissertation.

Chapter 4: Discussion

4.1 A survey of cancer pain control by South West England palliative care teams

4.1.1 Patients recruited

The numbers recruited to the pain survey show that relatively large sample sizes can be met in palliative care studies when multi-centre designs are used. However, as shown, this was a time-consuming process because of the research governance requirements. There has been debate in the literature about the perceived recent increase in bureaucracy and its likely impact on research output in the NHS.[176 177] Since this survey, changes have been made in order to assist researchers e.g. geographically linked R&D departments are now offering a streamlined R&D approval process, where only one application is made to a designated "lead" R&D department. In addition, some R&D departments are providing much more assistance with completion of the paperwork than was available before e.g. in obtaining key approval signatures from relevant personnel within hospital trusts.[178]

In this study, the numbers of patients recruited at each site was generally far less than the numbers anticipated by teams based on their normal daily workload. This, along with the very small numbers of refusals, possibly suggests that some gate keeping by the professionals recruiting to the study took place i.e. not all patients seen on the day were asked to participate. This may have been to comply with the protocol which stated that patients who were too distressed or not well enough

should not be asked about the survey. It is also possible that not as many patients were actually seen as was anticipated. On the day St. Peter's Hospice in Bristol were recruiting, several of the community nurses had their planned visits altered because of patients cancelling appointments due to unexpected hospital admissions. In future projects, the only way to be able to discern whether or not patients were being purposively selected would be to ask participating professionals to keep a log of all patients seen on the day and to note reasons for not approaching patients. However, this is likely to add to the documentation for a project and may be perceived as onerous by professionals trying to incorporate a research study into a normal working day.

A high percentage (84.3%) of patients participating had pain. Pain prevalence was highest in the outpatient setting (100%), followed by in-patient hospice (94.4%) and hospital (88.2%) then home (78.7%) and was lowest in day hospice (73.8%). These high percentages may be further evidence of selection bias having taken place although they are in line with other pain prevalence studies in palliative care populations.[12 65 179] The majority of patients had nociceptive pain (57.2%) or mixed pain (38.4%). Only 2.4% were thought to have neuropathic pain only. Again this is in keeping with other studies.[14]

Patients were recruited to the study in equal numbers from all settings except that fewer patients were recruited from outpatient departments. This reflects palliative care practice, where community nurses see most outpatients in their own homes, rather than suggesting large groups of outpatients were missed. A wide range of primary tumours were represented and the majority (77%) of patients with pain

were ECOG performance status 0 – 2. Only 5.7% of patients had a performance status of 4 (unable to get out of bed), but this was in keeping with the protocol where professionals were advised not to approach any patients who were considered too unwell to participate. Although the numbers of patients providing demographic data only were small, there were no differences in patient characteristics between them and those providing pain data, so there was no statistical evidence of selection bias. It is likely that the results are generalisable to the wider palliative care population and in particular to those who are of good performance status.

4.1.2 Control of pain

79.3% of patients had poorly controlled pain, defined as a worst pain score of ≥ 5. This was unexpectedly high and was worse than the results obtained from previous pain surveys using comparable methods.[62] [64] [65] Two pain surveys conducted in Israeli and American outpatients[180] [181] have reported similarly high levels of uncontrolled pain. Poor pain control was not associated with sex, ECOG performance status, setting or primary tumour site. Those with worst pain scores of ≥ 5 were 4 years younger, but it is unlikely that this finding is clinically relevant. There was weak evidence that longer time known to the palliative care team was associated with better pain control. The most important factors related to pain control were the occurrence of and number of breakthrough pains. 87.5% of patients with worst pain scores of ≥ 5 had pain flares, compared to 59.2% of those with worst pain scores of < 5 (p =<0.001). Those with worst pain scores of ≥ 5 also had more frequent episodes of pain flares (p = 0.003). It is impossible to know whether or not these pain flares represented transitory exacerbations of pain

in otherwise stable pain or whether they represented pain that was poorly managed. Those reporting pain flares had a higher mean pain on average score (difference = 2.3; 95% CI 1.1 to 3.3, p = <0.0001) and a higher mean pain now score (difference = 1.0; 95% CI 0.1 to 1.8, p = 0.01) possibly suggesting the latter.

One of the most interesting findings from the survey however, was the difference in proportion of patients with a research definition of uncontrolled pain and the proportion of patients who considered themselves to have uncontrolled pain. Only 14.2% of patients considered that their pain was not controlled, compared to 79.3% of patients who had a worst pain score of ≥ 5. This may simply suggest that the single question was not able to discriminate between good and poor pain control, perhaps because the expectations of patients are lower than that of their doctors. It was interesting to note that socioeconomic deprivation influenced the answer to this question, in that those in the most deprived areas were less likely to say that their pain was not controlled.

The original evidence that a pain score of ≥ 5 represented pain that was likely to substantially interfere with function is usually quoted as Serlin and colleagues.[63] They examined data accumulated from studies validating the Brief Pain Inventory in the United States, China, The Philippines and France and optimised cut-off points for grading worst pain scores as mild, moderate or severe, based on their impact on the mean pain interference score. The choice of worst pain score rather than pain now, pain on average or least pain was because pain worst had been shown previously to be more closely correlated to pain interference with function.[5] Other authors have confirmed this finding[179 181 182] with correlation

coefficients ranging from 0.39 to 0.64. Serlin and colleagues concluded that the best "fit" for cut-off points for the numerical rating scale were 0-4 to represent mild pain, 5-6 to represent moderate pain and 7-10 to represent severe pain, on the basis of the correlation coefficients obtained with pain interference scores. However, although this paper is usually listed as the reference for a worst pain score of ≥ 5 as representing a level at which pain significantly interferes with function, no such data are presented. This instead is found in an earlier paper[5] and the table in that paper supporting this cut-off point is shown below.

Figure 15: Table reproduced from Daut and Cleeland[5] showing the difference in interference score between worst pain scores of < 5 and worst pain scores of $\geq$ 5

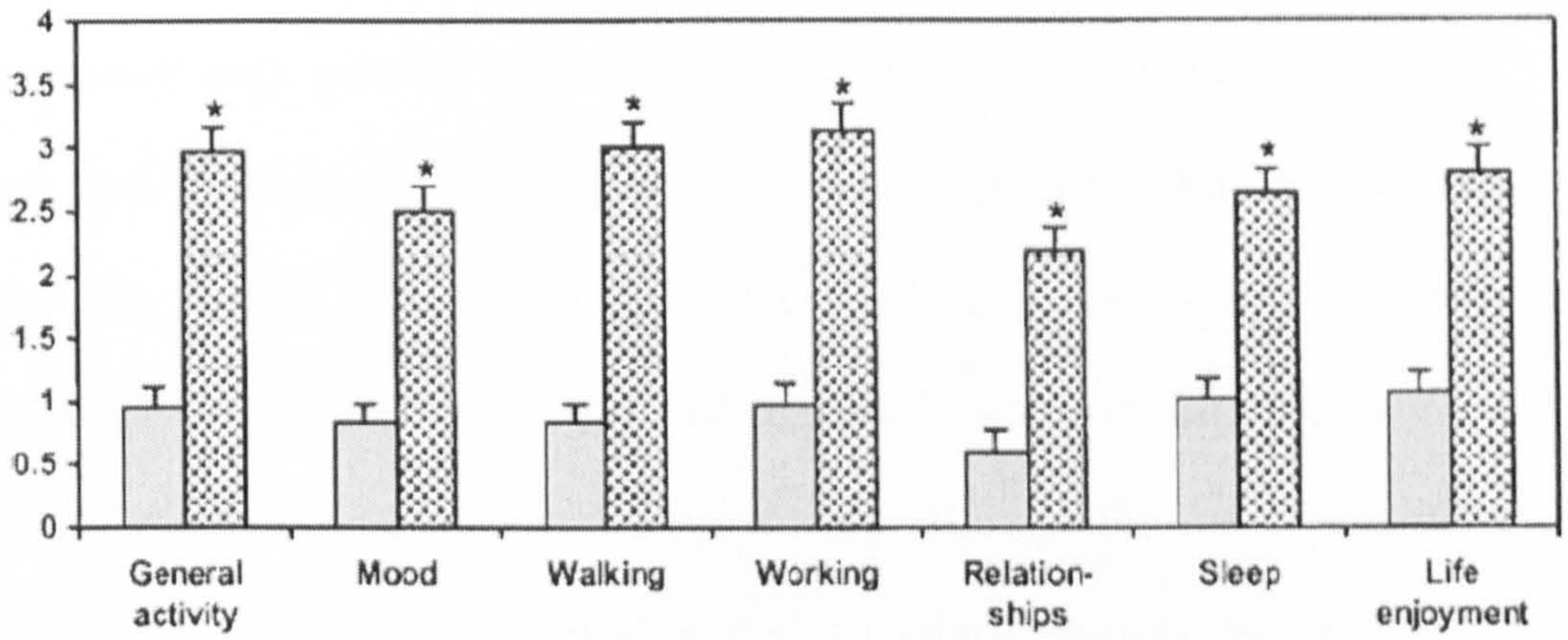
TABLE 4. Relationship Between Worst Pain Rating and Interference Ratings of Cancer Patients

Worst pain rating	N	Activity interference (Mean)	Enjoyment interference (Mean)
1	13	0.2	0.8
2	16	1.5	1.9
3	33	1.4	1.6
4	41	2.6	2.8
5	100	4.4	4.4
6	45	5.4	5.0
7	54	6.2	5.7
8	39	6.2	5.8
9	17	7.5	6.3
10	49	7.1	6.8

Daut and Cleeland[5] argue that because there is a greater jump in the mean activity interference score and mean enjoyment interference score between a worst pain score of 4 (activity interference = 2.6, enjoyment interference 2.8) and a worst pain score of 5 (activity interference = 4.4, enjoyment interference 4.4) than between other scores, then worst pain scores of ≥ 5 represent pain significantly likely to interfere with function and so proposed its use as a cut-off to represent

poor pain control. Potter and colleagues[118] investigated this further using a sample of 93 adults with cancer and came to similar conclusions when comparing those with worst pain scores of < 5 with those with worst pain scores of ≥ 5. However, as can be seen from their data below, the mean interference scores in both groups are low and we still do not know whether the differences in interference scores reported are clinically important to patients.

Figure 16: Table reproduced from Potter and colleagues[118] showing the differences in interference scores between worst pain scores of < 5 and worst pain scores of ≥ 5



Aspect of daily life	Pain intensity	*N*	Mean	Std deviation	Std error
General activity	< 5	62	0.95	1.06	0.13
	≥ 5	30	2.97	1.00	0.18
Mood	< 5	60	0.82	1.00	0.13
	≥ 5	30	2.50	1.01	0.18
Walking	< 5	62	0.82	1.09	0.14
	≥ 5	30	3.03	1.10	0.20
Working	< 5	62	0.97	1.27	0.16
	≥ 5	29	3.14	1.19	0.22
Relationship with others	< 5	59	0.76	1.02	0.13
	≥ 5	30	2.17	1.12	0.20
Sleeping	< 5	62	1.05	1.09	0.14
	≥ 5	30	2.63	1.03	0.19
Enjoyment of life	< 5	62	1.60	1.23	0.16
	≥ 5	30	2.80	1.06	0.19

Figure 1. Degree of interference with aspects of daily life; comparison between those with low and high pain intensity ($p < 0.000$ for all cases)

A telephone survey[183] asking the views of 287 randomly selected residents in Harris County, Texas about cut-off points to represent mild, moderate and severe pain on a 0-10 pain scale has confirmed that lay people describe similar figures to those obtained by Serlin and colleagues. However, our survey suggests that patients do not agree with the cut-off of ≥ 5 for worst pain as a level that distinguishes controlled pain from uncontrolled pain.

Whilst a great deal of methodological work has been conducted in order to validate pain scales for clinical trials and observational studies, very little work has examined what patients themselves see as the goals of pain management. Zelman and colleagues[184] conducted 11 focus groups with 53 patients experiencing chronic pain due to low back pain, osteoarthritis and metastatic cancer. Patients discussed achieving "manageable" pain days, because they did not expect their pain to be completely relieved. Manageable days were those during which pain was sufficiently relieved to allow them to concentrate on something else, when they were able to accomplish something, engage socially, obtain night-time rest and have a more positive affect. Undesirable days were those when pain restricted function, side effects of medication "eclipsed" the gains in pain severity, or when they were socially withdrawn because of pain with negative emotional consequences. The participants all considered it unlikely that they could achieve a pain score of < 5 without excessive side effects from pain medication and were generally critical of the use of pain scales in chronic pain. Further work would seem to be required with patients themselves, in order to explore the best way of measuring good pain control in cancer pain.

When initially piloting the patient questionnaire, several patients reported worst pain scores of 8 – 10, but answered that their pain was controlled. When questioned about this, they replied that when they had breakthrough pain, they took their breakthrough medication and it worked, and they perceived this to be controlled pain. This was confirmed within the survey results. 11/17 patients who said their rescue medication was not effective answered "no" to the single question, compared to 6/17 patients who answered "yes".

The presence of pain flares was not associated with responses to the single question, however the frequency of the flares was. As the frequency increased, so did the proportion of patients answering "no" to the single question ($p = <0.0001$). It seems likely then, given that frequency of breakthrough pain was a mediator of both an answer "no" to the single question and a worst pain score of >5, that control of breakthrough pain is crucial to pain control. Other studies have found high prevalence rates of breakthrough pain in cancer settings[185-187] and demonstrated that breakthrough pain is often difficult to predict, or if it is predictable (when it is often referred to as incident pain because it is provoked by particular incidents such as weight-bearing) it is usually difficult to treat because of its short duration. Zeppetella and O'Doherty[188] conducted a prospective survey of breakthrough pain in hospice patients and found that both the presence of breakthrough pain and its frequency predicted dissatisfaction with pain control. One of the pharmacological problems in the treatment of breakthrough pain is the rate of onset of analgesia from oral medication. A large proportion of breakthrough pains last less than 30 minutes,[188 189] but analgesia can take up to 40 minutes when the oral route is employed and can last for several hours, leading to

side effects (sedation in particular). Newer formulations of opioids with a quicker onset of action such as oral transmucosal fentanyl citrate (OTFC) are becoming more common, but are not without their own difficulties e.g. the transmucosal route is sometimes difficult to use in the presence of xerostomia. Another difficulty in the treatment of breakthrough pain is that there is no agreed consensus for the dose of opioid that should be used. In the UK, guidelines suggest using 1/6th of the patient's total 24 hour opioid dose. North American papers suggest 10-15% of the usual 24-hour dose, but data from the initial trials investigating the use of OTFC[190] suggest that a rigid schedule is not appropriate and as Portenoy and Hagen[189] amongst others suggest, breakthrough analgesia should be titrated to effect. Other treatment modalities such as radiotherapy or interventional procedures are often necessary to manage breakthrough pain and 30% of patients in this survey had received radiotherapy for pain control.

4.1.3 Use of drugs/other treatments

It was reassuring that only 15% of patients had a negative Pain Management Index and that this was not associated with poor pain control as it has been in other studies.[62 64] The percentage of patients taking a Step III opioid for pain control (66.5%) was expected.[56] Just over half of patients were taking morphine (52%), with fentanyl (22%) and oxycodone (20%) the other two most frequently used opioids. Only 4% of patients were being given diamorphine for pain control, but this probably reflects the national shortage of this drug when the survey was conducted. No patients in this survey were taking methadone for pain relief.

The use of adjuvants was less than anticipated. Less than 20% of patients were prescribed either steroids or anti-depressants, and less than 10% were prescribed anti-convulsants. This is lower than in other studies[191] but higher than in others.[192] Klepstad and colleagues[13] found regional differences in the use of adjuvants between 21 European countries participating in a cross-sectional survey. These differences may be explained by regional access to medications, but if not, suggest the WHO ladder is not used in the same manner by all professionals treating cancer pain, as was originally intended. 9.9% of patients were using bisphosphonates for pain relief, but this probably reflects the limited data supporting their use in pain relief from bone metastases.[193] What cannot be assessed in this survey however is adherence to treatment which has been shown to be a significant mediator of worst pain.[105]

It seemed that very little use was made of interventional techniques in the survey population. Linklater and colleagues[194] reported similar rates after conducting an audit of their own practice of interventional techniques. However, following a regular weekly session with an anaesthetist specialising in pain management their epidural rate increased from 1.9% to 5.4%. Very few units responding to their questionnaire about the use of anaesthetic services had formal links with anaesthetic colleagues, and most were satisfied with informal "as required" input. Informal links may mean that we are not always aware of what our anaesthetic colleagues can offer and patients' pain management options are limited as a consequence. This may be of particular relevance to the control of breakthrough pain where pharmacological management is currently limited.

4.1.4 Implications of the results: achieving desired sample sizes

One of the most promising results of the survey was that the sample size was almost achieved and so the estimates for the proportion of patients with poor pain control were obtained within narrow confidence intervals, improving their authority. Fostering research links with geographically connected teams seems to be a suitable way forward for achieving numbers required in other studies and will hopefully be facilitated by recent developments within NHS R&D departments.

4.1.5 Implications of the results: pain control

These data suggest that we cannot be confident in the estimate of 80% of patients achieving adequate pain control with use of the WHO ladder. The discrepancy may have arisen because of the methodology of the validation studies, with short follow-up in the studies leading to an overestimation of its success. Alternatively, it may suggest that the 80% figure can only be applied to patients with low complexity of needs and hence not those seen currently by palliative care teams. Repeating this survey across oncology inpatient, outpatient and day unit settings would allow us to assess this by comparing the proportion of patients with a worst pain score of ≥ 5 in all groups. However, when others have conducted surveys across all settings, the figure of 80% has not been verified.[62 64 65] The high percentage of patients with poorly controlled pain also seems to be contrary to the results obtained in both arms of the 2-step trial, where in the first 28 days, patients recorded a score of 4 or less on approximately 60% of days in the 3-step approach and 71% of days in the 2-step approach. This apparent difference may simply be explained by the use of "average" pain scores as an outcome measure in the 2-step trial and not "worst" pain scores. The difference may also reflect the intense pain

monitoring and frequent patient-professional interactions that took place during the 2-step trial, that are unlikely to be replicated in usual practice. A definitive 2-step trial should perhaps include a follow-on phase, where recruits continue to monitor daily pain scores, side effects and use of breakthrough analgesics, but with less contact with the research team. This might allow the continuing efficacy of both approaches during more "usual care" circumstances to be measured.

4.1.6 Implications of the results: clinician versus patient desirable outcomes for pain control

The most unequivocal finding from this survey was that the patients themselves did not agree with a research definition of poor pain control. Whilst there is clearly a positive correlation between worst pain scores and pain interference with function it is possible the evidence for the cut off of a worst pain score of ≥ 5 is perhaps not sufficiently robust. Whilst pain scores are necessary in order to compare two approaches or two different analgesics, it certainly seems that we should seek the views of patients about how to measure good pain control for observational studies on cancer pain.

4.2 Oxycodone for cancer-related pain: meta-analysis of randomised controlled trials

4.2.1 General findings

One of the most significant findings from this review was the lack of high-quality evidence available for synthesis in the meta-analysis. Only six studies were retrieved, and only four studies provided analysable data, representing 160 patients in total. The trials were of short duration, lasting between 10 and 20 days. Both of these reflect the difficulties of conducting clinical trials in this group of patients[150 151] where high attrition rates lead to pragmatic studies of short duration in order to minimise the losses to follow-up.

4.2.2 Effectiveness of oxycodone

The 95% confidence limits for the effect of oxycodone versus morphine are narrow. The upper limit of the confidence interval is consistent with a difference of only 6 mm on a 100mm visual analogue scale and the lower limit is consistent with a difference of 0.5 mm. For oxycodone versus hydromorphone the equivalent figures are 0 and 6 mm. These differences are much lower than those that are suggested to be meaningful to patients (a change of 20mm on a 0-10 pain intensity scale[195]). Therefore, in spite of the small number of studies we can exclude any clinically important differences in effectiveness between oxycodone and morphine and oxycodone and hydromorphone.

4.2.3 Tolerability of oxycodone

In view of the short trial durations, data on longer-term tolerability is not available, but the results demonstrate that there is no evidence of a difference in the tolerability of oxycodone and either hydromorphone or morphine. These studies provide adverse event data for dose titration phases of Step III opioids, which is important information for clinicians managing patients with cancer pain. It means that they can inform patients of the likelihood of experiencing early side effects and also reinforces the need for appropriate management of these side effects. The percentage of patients experiencing side effects and discontinuing treatment due to adverse events in the studies included in this review was considerable and in line with discontinuation rates from other studies of opioids in both cancer and non-cancer populations.[83 196-198] As the presence of side effects is one of the reasons patients are unwilling to continue or increase doses of pain relief medication[68] these findings re-emphasise the need for active questioning about, and aggressive management of, opioid related side effects.

Clinical experience suggests that the side effect profile of opioids does change with time, in that patients tend to develop tolerance to the sedation, nausea and respiratory depressant effects of opioids[199] but few studies are ever long enough to measure actual rates of continuing side effects. A comprehensive systematic review by Chou and colleagues[197] could not find any evidence to prove one controlled-release opioid had superiority over another in the chronic pain setting.

4.2.4 Trial quality

The study reports did not allow us to be confident about the internal validity of the trials. Only the Heiskanen trial reported an attempt to conceal treatment allocation, stating that the hospital pharmacist held the codes for treatment allocation. However, inadequate concealment of treatment allocation is usually associated with an exaggeration of treatment effect,[152] and so would not explain the absence of differences between oxycodone and control group that we found in our meta-analysis. In each of the included studies, patients who withdrew for any reason were not included in the final analyses comparing pain scores between oxycodone and control (Table 15). Attrition bias might further threaten the validity of the individual studies, but the discontinuation rates due to adverse events were similar for both oxycodone and control groups in all studies, so it is unlikely that it has influenced the results of our meta-analysis. Each trial reported that patients in both treatment groups had their opioids titrated in a similar manner until stable doses were obtained so there was no evidence of performance bias.

4.2.5 Generalisability

The studies recruited mainly from hospital communities, with pain from a variety of cancers, so it is likely that the patient population is representative of patients with cancer-related pain and that the findings can be generalised to this patient group. It is unclear whether or not the findings are relevant to other pain management settings. Three recently published systematic reviews[196-198] have demonstrated the effectiveness of opioids for pain management in the chronic, non-cancer pain population. Chou and colleagues,[197] in a systematic review of the comparative efficacy and safety of long-acting oral opioids for chronic non-cancer

pain did not retrieve any papers directly comparing oxycodone with other opioids in these patients. Eisenberg and colleagues,[196] in a systematic review of opioids in neuropathic pain, did not retrieve any papers that compared one opioid with another. The Kalso systematic review[198] only included trials comparing opioids with placebo, so no data were retrieved on direct comparisons of one opioid with another. All of these reviews confirmed the efficacy of opioids in a variety of chronic pain conditions and demonstrated that adverse effects are as common as in cancer populations, but no studies comparing oxycodone with other Step III opioids have been conducted in patients with non-cancer pain.

4.2.6 Implications for practice

Morphine, in both normal-release and modified-release formulations, has been the first-line opioid in the United Kingdom for the management of moderate to severe cancer pain. In this review, we did not find any important differences between oxycodone and morphine. Oxycodone is almost four-times more expensive than morphine in the UK and there is less general experience of its use. This is likely to be the case worldwide also, apart from perhaps the United States, where it remains more expensive but has been used more widely. Thus, there is no reason to challenge the recommendation to use morphine as a first-line agent for cancer pain. However, there is a need for larger trials of longer duration designed to obtain comparative efficacy and adverse event data for Step III opioids in both cancer and non-cancer populations.

There is no reason to assume that any one opioid should be superior to another at a population level, but one Step III opioid may be a better option than another at the

level of the individual patient.[200] Riley and colleagues[201] have conducted a prospective study investigating the characteristics of patients who require a switch from morphine. Although this study has limitations (there were no 'a priori' guidelines for deciding when to switch opioid and no information about any measures taken to control side effects other than the opioid switch was given in their paper) some genetic factors emerged as possible predictors of those patients who might need an alternative to morphine.[202] The information obtained in this review confirms the place of oxycodone as a suitable alternative to morphine in those individuals who become intolerant to morphine.

The increase in prescribing of oxycodone that was highlighted in the introduction may be explained by some professionals believing that oxycodone is a superior alternative to morphine after the experience of seeing an individual patient's side effects disappear following a switch from morphine to oxycodone. Anecdote is a powerful factor in our treatment choices but as palliative care professionals, we should educate our generalist colleagues that a successful opioid switch for an individual does not confer superiority to the alternative opioid used at a population level. It is likely that though that for some, oxycodone may remain a first line opioid by virtue of the fact that it is not called morphine.

4.2.7 Conclusion

It is important to be clear about the value of this meta-analysis. Our original aim was to display the accumulated evidence to date on which current prescribing patterns are based, highlighting both its strengths and limitations. The systematic retrieval, assessment and presentation of results of trials are crucial if clinical

practice is to meet the aim of being evidence-based. The combination of studies in a Forest plot and meta-analysis has a number of aims, not just restricted to the final pooled estimate: a) presentation of the results of all the included studies in one figure with easily accessible study-specific effect sizes and their confidence intervals; b) assessment of whether the results are heterogeneous (we found I^2 = 62%, heterogeneity p = 0.05); c) meta-regression allows sources of heterogeneity to be investigated (we demonstrated that the type of control may be a source of heterogeneity; p for difference in effect estimates = 0.1). If the results are consistent with each other (we showed that when studies were stratified by type of control group, they were), the final pooled estimates provide an appropriate summary statistic, on which to make (in combination with a critical analysis of the quality of the papers, clinical heterogeneity etc.) evidence-based, systematically obtained conclusions. Our conclusion would be that there is no current evidence to support the use oxycodone as a first line Step III opioid for all, but that for some patients who are intolerant to morphine, oxycodone is a good alternative.

4.3 The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

This section of the discussion chapter will consider the results of the 2-step trial and in particular consider factors relating to the feasibility and design of a definitive study to compare a 2-step approach versus the traditional 3-step approach. The results will be compared with the validation series studies and also with other trials comparing alternative approaches to the 3-step ladder.

4.3.1 Feasibility: trial recruitment

One of the most interesting findings from the recruitment figures in the CRUK pilot study was the difference in recruitment rates between the three centres involved. Whilst this may be in part related to the length of time the study was open in each centre, this is clearly not the only explanation. Recruitment in Bristol was at a rate of 1-2 patients per month. Oncology and palliative care colleagues from within hospital, hospice and community settings referred patients for the trial. Having ethical approval to visit and recruit patients in their homes undoubtedly facilitated recruitment of these patients, if only for pragmatic reasons such as the notorious difficulty of parking at Bristol Haematology and Oncology Centre (BHOC). It is unlikely that all of the patients we recruited in their homes would have entered the pilot study if they had been asked to attend the BHOC. Another difference between recruitment at Bristol, Edinburgh and Nottingham was that the research team at Bristol was dedicated almost exclusively to the 2-

step study. This meant that they were able to regularly screen patients' notes prior to key oncology clinics which served two purposes: it helped identify potential recruits but also raised colleagues' awareness of the study. Having a trial-dedicated palliative care research team also meant that we were available to provide pain consultations at short notice, even if a patient was eventually considered ineligible for the trial. Assisting colleagues with difficult pain problems seemed to increase the likelihood that they would remember the trial in the future. Another factor that may have been relevant to the differing accrual rates was that we raised the issue of fear of opioids early in the recruitment process with patients in Bristol, in order to mitigate its impact on trial refusals. This approach was suggested to us by the Quartet (Qualitative Research to Improve Recruitment to Randomised Controlled Trials) study group at the Department of Social Medicine in Bristol. It seemed that these key differences between the centres could explain the recruitment rates observed and means that a definitive study should apply for funds to have dedicated personnel at each recruiting site.

It was disappointing that no patients were recruited from primary care settings. Only two potential recruits were identified from the eight participating practices but neither entered. One was ineligible because of drug sensitivities and the second declined after reading the patient information sheet. The research governance process and the visits to individual practices had been extremely time-consuming during the set-up of the trial, and this did not seem to have been an efficient use of time or resources. We have been unable to explore reasons for this since only one of the participating practices has replied to recent email

correspondence about the trial. The definitive study could still consider participation from community settings, with the trial team having honorary primary care trust contracts, but it seems more likely that community palliative care teams will refer patients than primary care teams.

4.3.2 Design: use of diaries

The patient assessment booklet or diary seemed a useful tool with which to record pain data. Minimal data were required, which means that notation was less onerous for the patient and this possibly increased compliance with its use.[203] Those who wished to write more could do so. In fact, some patients continued to use a pain diary after they had completed the trial in order to keep a record of their pain control.

4.3.3 Design: additional contacts

The recruits in Bristol had an average of 3 extra contacts with the study team during the first 28 days. The majority of these were telephone contacts and were related to pain control or adverse events. A definitive study should incorporate these additional visits into the study design.

4.3.4 Design: attrition and missing data

Patients provided a mean of around 21 days of pain scores in the first 28 days of the study. When each day's pain score was considered, 825 data points from 37 patients were obtained. The majority (55%) of patients recruited to the CRUK study completed all 28 days as did 61% of patients recruited to the Napp study. This compares favourably with rates quoted in a systematic review[204] of attrition

in palliative care studies of between 34-80%. It seems then that a study period of 28 days is appropriate, since this will result in about 21 days of pain scores per individual and a significant proportion of patients will complete the study.

4.3.5 Design: utility of the outcome measures

The percentage of days when each individual recorded a pain score of 4 or less seemed to have the ability to detect a difference between the two approaches, but it is difficult to know what difference in percentage points would be clinically meaningful to patients. It seems appropriate to consider using a pain score of ≤ 4 as a cut off point for a definitive study comparing two approaches to pain management, since several studies including those asking patients themselves have confirmed that this represents "mild" pain.[63] [183] [205] This might seem to contradict arguments used against this cut-off point in the pain survey discussion (4.1.5) but the crucial difference is that a definitive trial would be comparing the difference in the percentage of time a patient records "mild" pain between the two approaches, rather than the difference in pain "control" between the two approaches.

4.3.6 Design: difference in Napp and CRUK studies

The mean proportions of time with a pain score of ≤ 4 were 53.6 (3-step approach) vs. 56.8 (2-step approach) in the Napp study and 63.7 (3-step approach) vs. 87.9 (2-step approach) in the CRUK study. This means the difference between the two approaches was 24.2 percentage points in the CRUK study vs. 3.2 percentage points in the Napp study. Thus, the overall proportion of days with a score of ≤ 4 was lower in the Napp study as well as the difference in proportions. Although the

test for interaction between the funders was not significant, it is unlikely that that the test had sufficient power to detect a difference. These differences may be explained by the observed regional differences in pain management and the fact that many different teams were recruiting to the Napp study compared to the CRUK study. If a definitive study is not to be confounded by such differences, then the use of analgesics will need to be controlled within the protocol and the number of personnel recruiting should be limited. This means requesting a research grant to concentrate the study on fewer sites, but with sufficient manpower at each site e.g. a half-time dedicated trial nurse. This should allow a difference between the approaches to be detected if a difference exists.

4.3.7 Pain results

The results show that pain scores were ≤ 4 for the majority of the time in both arms of the trial. This suggests that pain was mild for the majority of the time in both approaches and is somewhat at odds with the findings from the pain survey, although this might have been due to the different pain scores being recorded (average vs. worst). Pain control was possibly better in the study than it might have been in usual practice though, a finding that has been observed repeatedly in other research studies and is referred to as the Hawthorne effect[206] and perhaps provides justification for including patients at their end of their lives in research studies.

The results of all of the outcome measures suggest that the 2-step approach results in better pain scores for patients. Those randomised to the 2-step approach spent a greater proportion of the first 28 days with a score of ≤ 4, were more likely on any

day to have recorded a score of ≤ 4 and achieved stable pain control (four consecutive days with a score of ≤ 4) more quickly. These differences were of a magnitude that is likely to be clinically meaningful, but were not statistically significant probably because of the small numbers in the pilot study.

Brief pain inventory scores for least, worst, average pains and pain now were also better in the 2-step approach and these results were statistically significant. The difference for worst pain scores was also clinically significant, with an adjusted difference of 2.3 points on a 0-10 scale.

4.3.8 Adverse events rate

It was important to compare side effects in the two groups to ensure that improved pain control was not achieved at the cost of greater side effects. Overall the adverse event rates were low, which was reassuring but meant that it was not possible to compare the two approaches. Other studies have confirmed that introducing Step III opoids to opioid-naïve patients can be done safely.[130-133]

4.3.9 Patient-acceptability of the 2-step approach

The adverse event rate clearly has an impact on the patient-acceptability of the approach and it was therefore promising that these rates were low. However, it is likely that a number of patients will have been deterred from entering the study because of the negative associations with Step III opioids that were highlighted in the interview study. This has implications for recruitment to a definitive study and is considered in the discussion of the qualitative study.

4.3.10 Comparison with the results from the validation series

The finding that only three of the patients randomised to the 3-step approach during the CRUK funded study remained on a Step II opioid by the end of the 28 day period is consistent with findings from the validation studies.[48 56] It is difficult to compare the primary outcome of this study with the validation series studies however, because of the variety of outcomes used in those studies.

4.3.11 Comparison with the results from other studies investigating other approaches

This study adds to the evidence that alternative approaches which involve the earlier introduction of Step III opioids may be superior to the 3-step WHO analgesic ladder. Maltoni and colleagues[136] used a similar experimental arm to ours and found a statistically significant difference in the proportion of time spent with a worst pain score of ≥ 5 which favoured the 2-step approach. Similarly, in their study there was no evidence of an increased risk of side effects in the 2-step arm. Marinangeli and colleagues[135] reported a statistically significant difference in the mean change in pain intensity from baseline, favouring their experimental one-step approach as measured by a 0-10 VAS. However, the difference in mean change between the two approaches was only 0.68 cm and so the clinical relevance of this difference is not known. There was a greater incidence on nausea in the experimental approach, but the incidence of vomiting was not different.

4.3.12 Why might a 2-step approach be superior?

We had initially considered that a 2-step approach might be superior to the traditional 3-step approach for pragmatic reasons. Commencing a low-dose of a

Step III opioid as soon as Step I analgesics were no longer effective would mean only one change of medication, compared to the two changes to medication that are required in the 3-step approach (from the first to second and then second to third steps). This will mean that a community patient will need to contact a health professional twice. We also hypothesised that a 2-step approach would allow easier dose titration to provide pain control and also facilitate the use of escape medication since patients would have access to normal-release preparations of a Step III opioid as well as regular modified-release preparations. We became aware during the study that it was not usual practice to prescribe normal-release morphine for patients to use as escape medication in addition to Step II analgesics when necessary and in fact, one general practitioner initially refused to prescribe this for one of the trial recruits. Thus the 2-step approach meant that recruits immediately had access to regular medication and "breakthrough" medication, differing from the 3-step approach in usual practice, where patients are prescribed only regular Step II analgesics and may not have drugs available for breakthrough pain. The results of the interviews suggest it is possible that once the psychological barrier of commencing a Step III opioid is overcome, provided the initial experience is positive, they are taken more because patients' confidence in them will have increased. However, this was not borne out in the trial results, where the use of escape medication was less likely in the 2-step approach, but the confidence intervals were wide and consistent with both no difference and a greater use of escape medication in the 2-step approach.

The 2-step approach may also be superior because the addition of a Step II opioid to non-opioid analgesics does not provide sufficient additional pain relief, as has

been suggested by two previous well conducted systematic reviews of the use of non-steroidal anti-inflammatory drugs and Step II opioids in the management of cancer pain[125 207]

4.3.13 Conclusion

Thus, in light of the data obtained in this pilot study from both the qualitative and quantitative components, from other studies investigating the efficacy of the ladder and for pragmatic reasons, it seems a 2-step ladder should be compared to the traditional WHO 3-step ladder in a definitive, adequately powered controlled clinical trial.

4.4 A qualitative study to explore the views of patients considering morphine for relief of pain caused by cancer

The following part of this discussion chapter will address the results of the qualitative interviews. I will consider whether the information the interviews have given us can be applied to other patients with cancer pain being offered morphine or another Step III opioid for the first time i.e the generalisability of the results. My role as researcher will also be considered in the light of the findings. The results will then be compared to similar studies in the literature and then the relevance of each of the themes will be discussed within the context of both the pertinent social science and medical literature. I will conclude with what I consider to be the implications of the themes generated from the interviews for both clinical practice and further research.

4.4.1 Generalisability

It is likely the participants in these interviews were a representative group, since this was a study nested within a pain management trial and we were recruiting patients similar to those seen in clinical practice who were being offered morphine for cancer pain relief. I interviewed equal numbers of men and women and the age range was 55 – 80 years. I interviewed 12 patients within the 2-step trial and six patients who did not enter. Four of the patients not entering the 2-step trial also did not wish to be interviewed, but the most common reason for not participating in an interview was clinical deterioration. However, the views of all of the participants were very similar, irrespective of whether or not they entered the

clinical trial. What is not clear from these interviews is whether or not the themes generated would have been similar in patients with chronic non-malignant pain. However, given the dynamic nature of the themes described previously (Section 3.4.8), and the way in which the anticipation of death influenced the way morphine was seen as a last resort, it seems unlikely the results can be generalised to non-cancer populations, or at least to patients with pain due to conditions that are not life-threatening.

4.4.2 Reflexivity

It is not possible to know absolutely whether or not the strategies described in Section 2.4.6 of the methods chapter were successful in mitigating the effects of a doctor as researcher, but it seemed to me that these interviews were honest accounts of the experience of cancer pain. The participants told me what it was like to have pain, how their pain had been dealt with, the different approach they encountered when they saw palliative care professionals (including me, but not only me) and what being offered morphine meant to them. They told me how professionals had influenced their views on morphine (often negatively) and they even told me they might have been non-compliant during a clinical trial had they been given morphine. It did not feel during the interviews that they were telling me what they thought a doctor ought to hear although of course it may be that their experiences of pain management were even worse than they described. Perhaps for this study, my dual role served well. The interviews raised uncomfortable topics but the participants will have known I was used to hearing about death and dying and this may have made it easier for them to talk about their fears. Indeed, Hoddinott in her review of the opportunities and pitfalls of

being both a doctor and qualitative researcher gives examples of how her being a doctor facilitated discussion of topics deemed sensitive by the participants.[208] When discussing reflexivity, Malterud[175] suggests that a declaration of beliefs should be made at the start of a study. My a priori assumption was that the interviews would suggest autonomous individuals needed time to adjust to the idea of needing morphine, because of the fears described in the literature. The themes generated indicated that these a priori assumptions were wrong. It was unlikely therefore that my own views have biased either the interviews themselves or the process of analysis.

4.4.3 Comparisons with existing literature: general findings

These interviews showed us that for patients with pain caused by cancer, morphine is linked with death because of the manner in which they perceive it is used (in increasing doses resulting in sedation and shortened life). Those who do not consider themselves to be dying might therefore refuse it, in spite of the poor pain control they endure as a consequence. Whilst this association is strengthened by the anticipation of death that was prominent throughout the interviews, professionals themselves were described as the root of fears of morphine, particularly by suggesting morphine was life-shortening in some instances. The offering of morphine as a choice to patients was also seen as indicating professional ambivalence towards it as an option for pain relief. Previous experiences of side effects were important influences for patients in deciding whether or not to accept morphine. Those who told a story of a good outcome with either morphine or another Step III opioid spoke of how this helped to alter their perceptions of opioids and gave them confidence for the future. These

findings are important because they suggest that the fears of tolerance and addiction that predominate in the literature are not the most significant for patients. They also highlight the extent to which professionals foster fears about opioids. After exploring the literature in light of the data gathered, I located studies which substantiate the general findings from these interviews. Cohen and colleagues[209] purposively interviewed 10 patients they considered were "masquerading" pain as other symptoms. To the authors, these patients did not express their suffering as pain, instead reporting other overwhelming symptoms such as fatigue and anorexia, which seemed to respond to pain-relieving treatments. The interviews revealed a group of patients who were often unwilling to take pain relief medication, because of fear of side effects or lack of knowledge. As in my interviews, these patients all expressed an awareness that they were dying, but with differing directness. Pain relief was seen as shortening life ("*I know how hospice is and their treatment. I don't want to think about that because I don't want to die just yet. I want to live as long as I can*" p.186-187) and was sometimes refused. Schumacher and colleagues[210] conducted content analysis of transcripts of audio taped nurse-patient discussions during a randomised controlled trial of a pain management programme. The discussions involved 11 patients who consistently took less pain-relief medication than prescribed in spite of both uncontrolled pain and receiving coaching about pain control. Whilst the audio taped discussions cannot provide the depth my interviews did, they echo some of the themes, with fear of opioids stimulated by professionals and concerns expressed about previously experienced side effects. They also highlight the powerful influence of previous pain management experiences (their so-called autobiographies) on subsequent patient pain management behaviour and confirm

the need for patients' own stories of pain to be listened to by healthcare professionals.

4.4.4 Comparisons with existing literature: emergent themes

The four analytical categories derived from our interviews were anticipation of dying, morphine as a last resort, the role of the professional and "I haven't got any choice" but to commence morphine (or factors influencing the decision to commence morphine).

4.4.4.1 Anticipation of death

The participants spoke of the link between the presence of pain and thoughts about death, with pain a reminder of cancer and mortality. However, they had no knowledge of when they might make the transition to the phase of "active dying" so death remained probable rather than certain. This is congruent with studies already in the literature. Hinton,[211] reports a longitudinal interview study of hospice patients examining the process of acceptance of death. His data suggest patients and their families are generally more anxious about death when the timing of death remains probable rather than certain. Writing from his own personal experience, the sociologist and psychoanalyst Ian Craib[212] (Mortality 2003) describes how his own fear of death was submerged because it was impossible to live with it constantly; "the fear that I experienced was not, and is not when it now occasionally returns, something which can be faced at full intensity for very long" p.288. Vig,[213] reporting a qualitative study involving 26 terminally ill older men, describes how they would question the possibility of disease progression when a new symptom developed and that this might cause them to consider whether or

not they had moved to a phase of active dying. Adelbratt and Strang[214] also describe a similar phenomenon when reporting the results of interviews with 20 patients with brain tumours. They comment "anxiety that was related to the awareness of their terminal disease was easily triggered" p.502. Trigger phenomena in their study were things associated with cancer such as hospital smells and headache.

It is easy to see how pain experienced by people with cancer becomes a trigger for anxiety about death. Pain is probably the most feared consequence of cancer[31] and in his description of modern dying, Field[215] emphasises cancer as "the metaphor for the feared death" (p.256) in current British society. This is because of the perception of cancer death as untimely, unexpected and that the terminal prognosis is often established with relative precision, even if the time of death is harder to predict. Another feature of modern dying is the open awareness which characterises especially cancer deaths, so individuals with cancer know at some point in the future they will enter a dying phase, as in my interviews, but do not know when they might die. This is seen as a change from death in earlier periods of history e.g. the Middle Ages where the script was shorter and better known i.e. death within days from an infectious disease where the clergy and church were involved, instead of the doctor. Modern deaths also differ by being more individualistic, following the individual's own choices for a "good death", or individuals "writing their own script".[216] Whilst this fits with our increasingly individualistic society and the current emphasis of palliative care in the United Kingdom in promoting patient autonomy, this does however mean that for any individual the script is unknown.[216] Field[215] also proffers another of the

characteristics of modern dying as there being no "rites of passage" to signal the person's transition to the dying role.

4.4.4.2 Morphine as a last resort: patients

In this study, the participants read in the patient information sheet for the 2-step trial about a painkiller similar to morphine for their pain. The words they used to describe the emotions experienced when being offered morphine were "frightened" and "fearful". When this was explored it was clear they were interpreting the commencement of morphine as a rite of passage to a dying phase, because they believe the dose will be increased until morphine itself becomes the cause of death. The role of doctors and nurses in shaping the experience of modern dying[215] may also explain morphine being seen as a "rite of passage" since it will be almost exclusively these professionals who offer morphine to patients with cancer pain. That patients with cancer view starting morphine as a death sentence is previously documented in the literature but only as comments from experts in the field.[124] There have been very few data from patients themselves describing this, although associating morphine with a poor disease outcome was described briefly in the initial qualitative phase of the development of the Pain Opioid Analgesic Belief-Cancer Scale.[119] The equating of morphine with a short prognosis was not included in the updated Barriers Questionnaire II[115] however, and so more recently this has been lost from the literature as representing a common fear about opioids and as a reason why they are refused by patients.

It could be hypothesised that the refusal of morphine represents denial of death; some of the participants seemed to state they were attempting to do this; "it's just if I take more of this then I'm getting worse...and I don't want to get worse". This would not explain why some did choose to accept morphine as a painkiller, except of course denial of death is not a dichotomous condition, with denial and acceptance mutually exclusive states. Weisman[217] talks instead of a "middle knowledge", a state of unpredictable shifts between open acknowledgement of death and its repudiation. Perhaps what we see in these interviews is an attempt at a temporary repudiation of death by patients refusing morphine, such as when Gloria states "give me another 10 years and I'll take the morphine if you like". In their study examining the use of denial and acceptance as coping strategies by hospice patients, Copp and Field[218] describe how "denial serves to preserve self-esteem...and prevent disintegration and chaos at certain periods of the dying process" (p.126). Perhaps for some of our patients who were anticipating active dying because of being offered morphine, a self-protective denial of this anticipated death was accomplished by a denial of the necessity of morphine, albeit temporarily.

However, this discussion should not focus solely on the nature of awareness and acceptance of death. Whilst these may be pertinent in the context of the use or acceptance of morphine by persons with cancer pain, to write at length about awareness and acceptance of death would be to ignore the crucial finding from the interviews that the offering of morphine was synonymous with active dying to patients. The participants associated the use of morphine with dying because of the belief that relief of pain was traded for loss of function and hastened death.

Further evidence of the perception that pain control required this trade-off was found in a study exploring non-professional perceptions of a good death using interviews with both patients with cancer and relatives of patients who had died in a hospice.[219] Masson describes how pain itself was not an issue; what seemed important to the participants was how its treatment impacted on the achievement of other goals. One relative described her mother as being "really spaced out" and attributed this to morphine. She explained that her father had been "very aware" until his death and said this was a manner of death she would choose for herself, "even though it's in pain" (p.204). The hastening of death by increasing doses of morphine was not judged to be a wrongdoing by the participants I interviewed. Whilst this may have been explained by my small sample, it is supported by the results of a focus group study with older people about end-of life preferences conducted by Seymour and colleagues[220]. The general preferences of these older people were for "comfort care" as opposed to life prolonging measures and morphine was seen as an important factor in providing a good death. Excerpts of their transcripts, like mine, demonstrate how the margins between acceptable pain relief and hastened death are blurred in laypersons' minds (as they would seem to be for some professionals also). Again, the participants in Seymour's study deemed the hastening of death by morphine as being acceptable and not the same as euthanasia, more of an "easing the passing". Another similarity was that the links the participants made to the word morphine were "cancer", "pain" and "death" and that it was seen by some as a "last resort for people dying from incurable cancer". Although positively viewed as a comfort measure, this also meant it was not viewed as a medical intervention for the relief of pain in any other setting. It was noted that professionals had reinforced some of these views,

with one of Seymour's focus group members recalling how a doctor had told her that continuing to give pain-relieving drugs "lessened the resistance".

It may be that patients face modern death without familiar scripts or role models, and this leaves a gap for a "rite of passage" to active dying, such as the commencement of morphine, to emerge. In my interviews, I found that professionals had enhanced the association of morphine with death and dying. In order to address this, we should consider why it might be professionals think and then say to relatives that Step III opioids hasten death, all the while "encouraging" their use, presumably under the aegis of the doctrine of double effect.[221] If I am to argue that morphine should not be synonymous with death, and if it were not, it would be more accepted/used/useful, then we need to examine the evidence that it does not cause death.

4.4.4.3 Morphine as a last resort: professionals

Professionals have concerns about the hastening of death with morphine because of the ability of opioids to cause respiratory depression. When used in acute pain or in overdose (such as when taken by drug addicts) or if the patient's clinical situation changes unexpectedly (e.g. the development of acute renal failure) respiratory depression does occur with opioids and can be life-threatening. However, the clinical impression of those working in palliative care is that respiratory depression is uncommon in their patient population.[199 222 223] Walsh and colleagues[222] conducted a small prospective study examining the respiratory function of 20 patients receiving in excess of 100mg of morphine daily and could not find evidence of respiratory depression. When blood gases did suggest

alterations in lung function (many of the patients had co-existing respiratory problems such as silicosis and bronchitis) these were not considered to be severe. This was supported by a recent Chinese prospective study[224] of the use of morphine in over 500 patients which showed an incidence of respiratory depression of only 0.2%. The absence of respiratory depression when morphine or other Step III opioids are used to treat chronic pain is generally explained by the tolerance to this side effect which is thought to develop. It is for this reason that opioids are not used in euthanasia.[225] Thorns and Sykes[226] report further evidence to support this theory. They conducted a retrospective analysis of the use of opioids in the last week of life in 238 consecutive patients dying in a palliative care unit. They showed that patients who received marked opioid dose increments at the end of life did not have shorter survival than those who received no increases, as would be expected if opioids hastened death by respiratory depression. Laboratory evidence also shows that pain stimulates respiration and so will attenuate morphine-induced respiratory depression.[227] This has been proven in studies with healthy volunteers[228] and has been postulated as the mechanism that explains case reports of respiratory depression occurring in patients who had been receiving stable doses of opioids, following the abolition of their pain by other means. In these case reports, successful techniques such as neural blockade have alleviated pain, thereby resulting in a loss of the antagonism of the respiratory depressant effects of the opioids.[229] [230] Thus, the antagonism of the respiratory depressant effect by pain and the tolerance that develops to respiratory depression in chronic opioid use suggest there is no reason to assume that morphine, if used correctly, will shorten life even if dose increments are required.

This pharmacological knowledge does not appear to have been translated into clinical practice outside of palliative medicine. In a 1997 survey of the attitudes of the American Society of Clinical Oncologists about physician assisted suicide and euthanasia,[231] a question was asked about the willingness of physicians to use escalating doses of morphine, sufficient to cause respiratory depression and end life in a patient with poorly-controlled pain. The physicians who would not consider increasing doses of morphine for a patient with excruciating pain because they thought respiratory depression was a possible outcome, were 0.61 (C.I. 0.48 to 0.77) times less likely to support euthanasia or physician assisted suicide. The authors suggest concerns about euthanasia and physician-assisted suicide inhibit the use of opioids by professionals, which results in uncontrolled pain for patients. At no time in their paper do they argue against these concerns. Evidence of negative attitudes to morphine was also found in a French national survey on palliative care[232] where 17% of HIV specialists either agreed or strongly agreed with the statement "prescribing high-dose morphine to a terminally-ill patient should be considered euthanasia" (p.624). The final sentence in this paper reads "Clearer guidelines are also necessary to avoid the confusion between morphine analgesia and euthanasia" (p.626). In an American qualitative study on end-of-life decisions,[233] nurses and physicians were asked to comment on an end-of-life scenario, within which the use of morphine is postulated to be facilitating death. Here the respondents felt that although respiratory depression was not absolute, patients receiving high-dose morphine for pain control have a compromised sensorium which often leads to hypoventilation and respiratory complications that may hasten death. During this study nurses expressed repeated concerns about the

high levels of morphine often used to relieve patients' pain, illustrated by the following quote from the paper:

I really struggle with the question of whether I am killing the patient because I am turning up his morphine drip and he is going to quit breathing. I can't quite do that. (p.620)

Reference to inevitable respiratory depression is also found in an article in the Journal of Palliative Medicine,[234] an American journal, when Jansen argues for involving patients in the decision-making process about pain relief. She advocates a scenario in which the physician involves both the patient and the patient's chaplain in ethical discussions about increasing doses of opioids, because of the risks of hastened death caused by respiratory depression that she argues should be communicated to the patient.

The patients in the interviews talked about the inevitability of increasing doses. In an educational paper on end-of-life issues in the Journal of the American Medical Association, a medical journal with one of the highest impact factors, a clinical scenario involving a Mr B, an 81 year old gentleman with pulmonary fibrosis is discussed, using excerpts of conversations with both him and his son.[235] During the discussions on treating his disease, the symptomatic treatment of his breathlessness is raised and "the promise of *gradually escalating* (my italics) doses of morphine" (p.2505) suggested for continuing dyspnoea. Another article echoing the words participants used in the interviews appeared in the British Medical Journal this year[236] when two American professors of public health and

family medicine described opioids as "a last pharmacological resort" for the treatment of osteoarthritis. This is in spite of two systematic reviews providing strong evidence that opioids have an overall clinically important benefit of about 2cm pain relief on a 0-10cm visual analogue scale in osteoarthritis.[198 237]

There is also evidence of the belief that morphine hastens death in the medical sociology literature. Timmermans [238] discusses the notion of "death brokering" by the medical profession and the concept of the "good death". He describes how "hospice workers aggressively treat thirst, bed sores, constipation and pain – even if the pain management with morphine might depress breathing (the double effect)" (p.998).

It is not only in the medical press that beliefs about the use of opioids at the end of life are promulgated. Following the publication of a paper by Seale[239] about end-of-life decisions made by U.K. medical practitioners, the Times correspondent Lister, ran an article entitled "Doctors 'hasten one third of deaths by using pain relief'". This was an incorrect interpretation of the Seale paper, in which the figure of 33% was given for the percentage of deaths in which the doctors participating in the survey considered the alleviation of symptoms had possibly shortened patients' lives. This figure therefore included the use of sedatives as well as opioids and referred to possible rather than probable or definite shortening of life.

It is interesting that the literature about respiratory depression caused by morphine and the routine use of escalating doses is mainly in the North American medical press; the concerns about opioids that once threatened the development of the

WHO ladder may still remain and prevent its proper use. However, it would be wrong to assume that only North American professionals have negative views about morphine. Seale's survey[239] showed that U.K. doctors believed the alleviation of symptoms possibly hastened death in 33% of dying patients they attended. In a subsequent editorial, Forbes and Huxtable[240] challenged both the methodology of the study and its conclusions. They comment on their experience that both clinicians and medical students often believe they are hastening death by the use of opioids at the end of life due to respiratory depression, when in fact the evidence suggests they are not. This year, in an anonymous personal view in support of the assisted dying bill published in Clinical Medicine, the journal of the Royal College of Physicians, the author (a doctor) described how his/her mother only received "proper terminal care" when she got to the hospice and " a morphine infusion ended her life".[241] Is it any wonder that Andy said: "the three words that strike the fear of God into your average working class bloke are 'morphine', 'palliative' and 'hospice'"?

It seems that many in both professional and lay circles share the view that the use of morphine is precluded until the dying process begins. This is further evidenced by the fact that much of the current literature around death and perceptions of a good death is consumed by discussions about pain relief.[213 242 243] In particular, the North American literature shows that fear of dying in pain is a significant issue for many.

4.4.4.4 Lack of concern about addiction and tolerance

It was interesting to note that when the participants were allowed a "free rein" to raise whatever they wished in the interviews, very little was made of addiction and tolerance. When addiction was mentioned it was because participants had heard of addiction in relation to opioids, but they found it difficult to say what addiction would mean to them. Only one participant mentioned tolerance, because he had read the patient information leaflet supplied with the bottle of morphine. Even then, he spoke of a need to increase the dose rather than the common concept of tolerance i.e. "if I use morphine now it will not work later when the pain is worse". Other participants talked of inevitable dose escalation but not because of a lack of effectiveness of morphine, rather because this was what they had seen happen to others. This did not seem to represent anxiety about eventual lack of effect of morphine. It is possible that addiction and tolerance have been perpetuated through the opioid literature because concerns about them are easier or perhaps "safer" to mention in research studies, especially quantitative studies, than fears about death and dying. It is also possible that the notion that patients are concerned about tolerance and addiction is itself a "myth about morphine".

4.4.4.5 Side effects

Another concern raised in my interviews and borne out in the literature was patients' fears about side effects. This is supported by a telephone survey conducted by Palos and colleagues [244] which also found that prior experience of side effects acted as a deterrent to the use of analgesic medication. In this study, 302 randomly selected adults were asked about prior experience of and knowledge about pain and therapy for pain relief and about their willingness to use analgesics

for differing levels of pain. The authors found previous experience of side effects meant an individual was 1.3 (95% C.I. 1.1 to 1.5) times more likely to be in the "conservative cluster" i.e. less willing to take analgesics for pain. The main side effects mentioned in our interviews were the neuro-toxic effects of mental clouding, sleepiness and hallucinations and these were seen by some as inevitable. In fact there is some evidence that being in pain has a more negative effect on psychomotor functioning than receiving stable doses of opioids.[245] Klepstad and colleagues[246] showed cognitive impairment (as measured by objective assessments) was not related to patients' self-reports of cognitive impairment and sedation, suggesting a more systematic observation of patients' cognitive function may be necessary in order to either reassure them that opioids are not associated with impaired function or to take appropriate measures if they are. A well conducted systematic review of the management of all opioid side effects[247] commented on the poor quality, weak evidence physicians have to guide their practice when managing opioid side effects. This lack of available evidence suggests side effects have not been considered a research priority in spite of their influence on patients' decision-making. If scant attention is paid to side effects or they are not managed properly, perhaps because the professionals think they are unmanageable, patients will continue to be deterred from using morphine or other Step III opioids.

4.4.4.6 Decision-making (factors influencing the decision to commence)

There were similarities in our interviews with results of other studies in the non-cancer pain literature about the factors that influence patients' decisions to take analgesics. Ross and colleagues[248] used focus-groups to discuss what strategies

older people use to manage pain and found they employed a variety of non-pharmacological strategies, seeing medicines as a last resort (no quotations are used in the manuscript so it is not known whether this was a phrase used by the members of the focus group or an interpretation by the authors). Participants' reluctance was in part due to the side effects experienced with analgesics. The decision to use a particular strategy was based on the severity of the pain, personal experience and self-acquired knowledge (including side effects experienced and whether or not a particular strategy had worked in the past). This also fits with a synthesis of qualitative studies of lay experiences of medicine taking conducted by Pound and colleagues.[249] This review concludes, "there is considerable reluctance to take medicines and a preference to minimise medicines intake" (p.151). The authors supported the tendency of the public to "resist" using medications (of all kinds) viewing this resistance as a reasonable consequence of the adverse drug reactions experienced by many, which they felt had been previously marginalized as patient-held "beliefs" about medicines. Horne and Weinman[250] explored the relationship between patients' beliefs about medicines and self-reported compliance and found that patients engage in cost-benefit analyses when deciding whether or not to use their medications. This could be extrapolated to the use of opioids as seen in this study, where one of the factors in commencing Step III opioids was the severity of the pain experienced. If the perceived benefit for the participants was freedom from pain, then this benefit was greater if their pain was severe. The costs perceived by the participants were likely to be side effects and perhaps even inevitable death and it may be that it was only when pain was "excruciating" that the cost-benefit analysis finally favoured the use of Step III opioids.

4.4.4.7 The role of the professional

The participants spoke of the difference in consultation style they experienced when they were seen by palliative care professionals who believed their pain, took the time to listen to their stories and demonstrated specialist knowledge. They also told how other professionals had influenced their decision to commence morphine. The impact of the professional on pain management has also been demonstrated in other studies. Sherwood and colleagues[251] asked a large sample of hospitalised patients about satisfaction with pain management using three open-ended questions at the end of a questionnaire survey. Patients were more satisfied with their pain management if health care providers "affirmed the pain experience…used expert knowledge and skills to manage pain and responded with caring, timeliness, and attentive presence" (p.493). The participants in my interviews also described language used by professionals that had helped them accept morphine or oxycodone and said they thought good explanations of opioids were essential. The need for detailed information about opioids, including a warning about side effects, was echoed in a focus group study of patients who had been using a patient-controlled analgesia device (PCA) containing morphine for post-operative pain control.[252] Chumbley and her colleagues designed the study in order to develop and evaluate a new patient information leaflet for patients using PCA. These patients felt they wanted detailed explanations about morphine, especially about side effects, so that if side effects did arise they could seek help. They also felt an explanation of the difference between opioids used in a controlled manner and as drugs of abuse would have helped.

4.4.5 Implications for clinical practice

4.4.5.1 The role of the palliative care team

The difficulties of pain management in busy oncology clinics, where the focus of care is on disease rather than symptom management, are highlighted in my interviews. In the oncology centre where these participants were recruited there is no routine measuring of pain scores. However, even in centres that have incorporated routine measurement of pain in the outpatient clinic, studies have shown pain management does not automatically improve.[253] Reyes-Gibby and colleagues[254] also demonstrated that patients might report different pain scores in different settings. Because of their study design, they were unable to draw definite conclusions about possible reasons for this differential reporting, but one possibility included patients being unwilling to report pain in places such as chemotherapy outpatient clinics, in case this led to treatment being interrupted. However, perhaps these findings, along with the stories of sub-optimal pain management told in our interviews, should provoke a discussion about the involvement of palliative care teams earlier in the patient's disease trajectory. It may be that the traditional model of frequent follow-up of patients by palliative care teams would not be appropriate, being replaced instead by intermittent consultations about pain management. The involvement of palliative care teams earlier in the disease trajectory may also help to dispel the fear that the word "palliative" invokes in some. Greater education and training of other professionals likely to be offering morphine to patients with cancer would also seem crucial to improving cancer pain control.

4.4.5.2 The role of the professional: offering morphine

The results of these interviews have implications for the language used by doctors when talking to patients about the management of cancer pain, because of the effect our words have on patients' decisions about painkillers. Further examples of the importance of language are found in the initial wording of the WHO ladder with the use of "weak" (Step II) and "strong" (Step III) opioids. Although the terminology altered in the 1996 version of the analgesic ladder, the words weak and strong have survived in common usage. In their analysis of the consultations recorded during a pilot study of a pharmacist as a medication counsellor Chen and Britten[255] found that perceived potency was important to patients, especially when dealing with side effects. If a drug was thought to be strong, but had unwanted side effects, then patients would most probably stop it, even if it were effective. It seems likely, as shown in my interviews, that language plays a part in decision-making about opioids and the use of the term "strong" is not helpful to patients when considering morphine or other Step III opioids. These results provide us with the evidence we need to educate both students and colleagues in terminology that makes Step III opioids less fearful to patients and about the importance of professional attitudes to morphine.

4.4.5.3 The role of the professional: side effects

The evidence from the literature review in the Introduction (Section 1.5) is that professionals believe that side effects from opioids are difficult to treat, or inevitable. The paucity of good evidence available about the management of opioid-related side effects also suggests that they have not been given priority, in spite of the evidence that they have a powerful influence on pain management

decisions made by patients. It is clear from the interviews that a negative experience of opioids can result in uncontrolled pain not only for that patient, but also for those in his/her social circle who may witness the event and later require Step III opioids themselves. The management of opioid related side effects must be exemplary if they are to be usefully employed in the treatment of cancer pain and professionals must be taught about both the monitoring of opioids and the consequences of poorly managed side effects.

4.4.5.4 The use of the doctrine of double effect

The doctrine of double effect is often employed to support or justify the use of opioids at the end of life,[256 257] in spite of commentaries[258 259] and evidence[226] suggesting it is not necessary to do so. Fohr[258] also argues that it is harmful to do so because to invoke the doctrine reinforces negative associations in the minds of both professionals and patients. I was interviewing participants at the same time as the Assisted Dying Bill was being debated nationally, and the doctrine of double effect was mentioned frequently by those against assisted dying, as a means of reassuring the public that pain can be controlled at the end of life. It seemed this debate was indeed reinforcing the association of morphine with death and dying for the study participants. At a recent educational event on ethics aimed at palliative care professionals, a scenario involving the possibility of a patient's death after the administration of analgesics was introduced in order to stimulate a debate about the doctrine of double effect. I would argue that there it is erroneous to use opioid analgesics as examples for the principle of the doctrine, because the evidence is that opioids do not shorten life and to do so reinforces the misconception that they do.

4.4.6 Implications for research

4.4.6.1 The value of qualitative methods

It is interesting to note that Sela and colleagues[260] after conducting a study asking patients to rate their pain and then their emotions experienced when in pain on seven different visual analogue scales, concluded that pain was not associated with fear in patients with cancer. The mean rating of fear was 36.8 (SD 26.4) for men and 48.5 (SD 29.8) for women, which was lower than the other emotions asked about (frustration, anger, exhaustion, helplessness and hopelessness). The correlation coefficients for physical pain and fear were only 0.05 (men) and 0.23 (women). In the light of these findings, they conclude "Contrary to popular belief, it appears that advanced cancer pain does not foster pronounced fear" (p.30). This is contrary to our results also, since the participants spoke of how pain reminded them of their disease and their impending death. Perhaps the use of qualitative methods is a more sensitive means of eliciting concerns such as fear of death.

4.4.6.2 Future projects

We know that knowledge about safe prescribing of opioids is reaching medical students when their curriculum allows (Forbes personal communication) but we do not know if their attitudes to opioids are altered when they become junior doctors on hospital wards and exposed to the attitudes of more experienced colleagues. We do not know whether the professional views about opioids demonstrated in these interviews belong to mature colleagues, or are in fact more widespread and present throughout senior and junior medical and nursing staff. The origin of professional concerns about Step III opioids must be investigated if we are to change attitudes, particularly if we might suggest their earlier use in

cancer pain as part of a 2-step ladder. Increasing regulation of Step III opioids[261] following the Shipman enquiry may lead to further inhibition of their use in primary care and this requires investigation.

4.4.6.3 Conducting a definitive 2-step trial

Whilst improving recruitment was not the primary aim of the qualitative component of the pilot study, we should make use of the findings when considering the conduct of the definitive 2-step trial. Other studies have shown that in a randomised study the language used and the manner in which treatment arms are presented to patients has an influence on recruitment rates.[262 263] My interviews have shown that patients have negative perceptions about morphine and other opioids that cannot be ignored when recruiting to a trial involving opioids. However, the interviews have also shown that careful use of language e.g. low dose and attention to side effects may mitigate against the effect of these perceptions. Furthermore, those discussing trials involving opioids with potential participants will need to be aware that the offering of morphine will be interpreted as a bad prognostic sign. It may be necessary to address this within the patient information sheet and certainly during conversations with potential recruits in order to maximise recruitment.

Chapter 5: Conclusion

Key conclusions

- Current approaches to the assessment of cancer pain need to be improved
- Current cancer pain control is sub-optimal
- A trial to compare the 2-step approach versus the 3-step approach is feasible and justified
- Education of professionals about both the application of the ladder including the use of adjuvant analgesics and judicious use of opioids is required even if no changes are made to the ladder
- The greatest barrier to the use of opioids in cancer pain is that patients associate them with death

The studies in this thesis have shown that whilst research in palliative care involves an often frail patient group, the difficulties this entails can be overcome by collaboration with colleagues to maximise recruitment, designing studies to minimize the additional burden on the patient and using a combination of methods to make maximum use of data obtained.

The studies have shown that it is likely that cancer pain management can be improved, but that we need to listen to patients first, in order to hear from them about their expectations and concerns about pain control. The systematic review showed, along with others[82 83 162] that it is unlikely that the use of an alternative Step III opioid to morphine as first choice will have a significant impact on pain management. The pain survey showed that according to current research definitions, almost 80% of patients had uncontrolled pain, but that the patients

themselves when asked did not agree that their pain was poorly controlled. The 2-step trial has provided evidence that an approach which omits the second step of the current WHO ladder and uses Step III opioids as soon as Step I analgesics are no longer effective, may mean improved pain control, although this must be tested in a larger randomised controlled trial. However, the interviews showed that if this approach is to be adopted, careful language will be required with patients themselves, in order to promote earlier use of Step III opioids.

We must remember that the WHO Ladder was designed to be used worldwide. Difficulties in accessing both Step II and Step III opioids remain throughout the world (http://www.eolc-observatory.net/global_analysis/regions_main.htm), both because of expense and concerns about diversification. However, it may be that the removal of the second step and sole use of Step III opioids would be acceptable as a worldwide approach, allowing efforts to improve opioid availability to concentrate on making morphine alone more easily available.

It seems that anecdote is a more powerful teacher than evidence for patients (and perhaps also for professionals) as demonstrated by Andy:

> all the information that I've got in my head has come from watching them, hearing about them and seeing them dying.

Earlier introduction of Step III opioids would mean more patients using them earlier in their disease trajectory. This may then provide the stories or images of people "living" with opioids and perhaps even "living better" with opioids if we

can ensure that they are used correctly and side effects are managed properly. The consequences of these stories might be to change this quote to

> all the information that I've got in my head has come from watching them, hearing about them and seeing them living

and thus might alter the perception that morphine is synonymous with dying. This, along with efforts to minimise the impact of opioid side effects both by studies investigating how best to manage them and education of professionals will surely have a positive impact on cancer pain control. Perhaps, rather than waiting for new approaches to be identified, we should begin to make best use of what we have available and consider a commentary in the Lancet from 1995 which stated

> "Morphine is a remarkably effective analgesic, and when used correctly, remarkably safe as well".[264]

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Appendix 1

Protocols for the field-testing of the WHO ladder

STUDY 2 OF THE PROGRAMME TO FIELD TEST THE WHO DRAFT INTERIM GUIDELINES HANDBOOK ON RELIEF OF CANCER PAIN

Paper prepared by Dr Richard Gelber, World Health Organization Collaborating Centre for Cancer Biostatistics Evaluation, Harvard University School of Public Health Boston, United States of America

CONTENTS

1. INTRODUCTION

It is estimated that over half of all cancer patients suffer needlessly from pain. Studies conducted in the United Kingdom and United States, where high levels of expertise a available, indicate that fully 25% of patients die with pain. The problem of inadequate control of cancer pain is even greater in the developing countries, where basic analgesic drugs are not available to 60-80% of the population.

Even when the means to control cancer pain are available, they are often not effectivel utilized. Administration at adequate doses is avoided even in suffering patients for fear o drug addiction and toxicity. A lack of understanding of the basic principles and methods already available to relieve pain contributes to the problem.

The World Health Organization (WHO) Cancer Control Programme has identified three major targets: to prevent cancer; to cure patients detected early; and to promote a good qualit of life and death with dignity for the 65% of patients who cannot be cured.

In 1982 the WHO Executive Board, Advisory Committee on Medical Research and World Healt Assembly endorsed the WHO Cancer Pain Relief Programme, whose objective is to offer pain relief to cancer patients through the existing health care system. In October 1982, a WHO consultation was held in Milan with a core advisory committee of experts in pain treatment. A document entitled "WHO Draft Interim Guidelines Handbook On Relief of Cancer Pain" was prepared. The principle objective of the present study is to field test these guidelines. Feasibility, compliance and effectiveness are the main endpoints for the evaluation.

In 1984, the WHO Collaborating Centre for Cancer Pain Relief was identified in the Division of Pain Therapy at the National Cancer Institute of Milan. This centre, in conjunction with the WHO Collaborating Centre for Cancer Biostatistics Evaluation at Harvard University in Boston, will coordinate the conduct of this study as the central operations office for the Field Testing.

2. SUMMARY OF THE GUIDELINES

The guidelines being tested are those described in the document dated 7 December 1983 and entitled "WHO Draft Interim Guidelines Handbook on Relief of Cancer Pain". These guidelines propose a therapeutic strategy for the effective use of drugs to treat cancer pain. After the assessment of the exact nature of the patient's pain, when specific pain relieving procedures (surgical or chemo-radio-hormono therapies) are not indicted or not available, treatment should be started at once with the pain relief drug or drugs carefully selected. Drugs have to be administered at adequate doses at fixed times, by oral route whenever possible. The drugs used for relieving cancer pain can be classified into four groups as shown in Table 1. The specific indications for use, recommended doses, and potential side effects are given in detail in the guidelines document.

The sequence of administration of these drugs will follow the course and increase in severity of pain with time, starting from nonnarcotic drugs, which represent the first step. When the recommended analgesic dosage and frequency fail to relieve pain, the medication should be strengthened by a drug of the weak narcotic group. If the weak narcotic and the nonnarcotic proves ineffective, a strong narcotic should be used. Especially in patients with bone pain, requiring additional analgesia, aspirin or other antirheumatics may be added to the narcotics. Adjuvant drugs should be used together with narcotic and nonnarcotic drugs in case of specific indications. The analgesic ladder, which illustrates the basic principle of treatment as defined by the guidelines, is shown in Figure 1.

THE COMPLETE GUIDELINES DOCUMENT MUST BE CONSULTED PRIOR TO INITIATION OF PAIN TREATMENT TO OBTAIN DETAILS OF THE APPROPRIATE REGIMENS TO FOLLOW.

The following seven points are indicated in the Summary of the Guidelines (page 25):

1. Cancer pain can and must be treated.

2. First, take a full history and examination and exclude acute conditions that require urgent treatment.

3. Drugs will usually provide good relief provided you use the right drug(s), the right dose(s), and the right frequency of dosage. The drugs must be given regularly by the clock and not on demand ("p.r.n.").

4. Start the patient on a nonnarcotic drug and adjust the dose to optimum level (see Guidelines Table III). If necessary, use an adjuvant drug in addition (Guidelines p. 20).

5. If or when this treatment no longer relieves the pain, administer a weak narcotic drug (Guidelines p. 10) in addition to the nonnarcotic and together with an adjuvant if necessary.

6. When this no longer relieves the pain, start the patient on strong narcotic therapy together, if necessary, with adjuvant drugs and other analgesics (Guidelines p. 20).

7. The patient must be supervised as often as possible to ensure that treatment continues to match the pain and to exclude side effects and toxic effects.

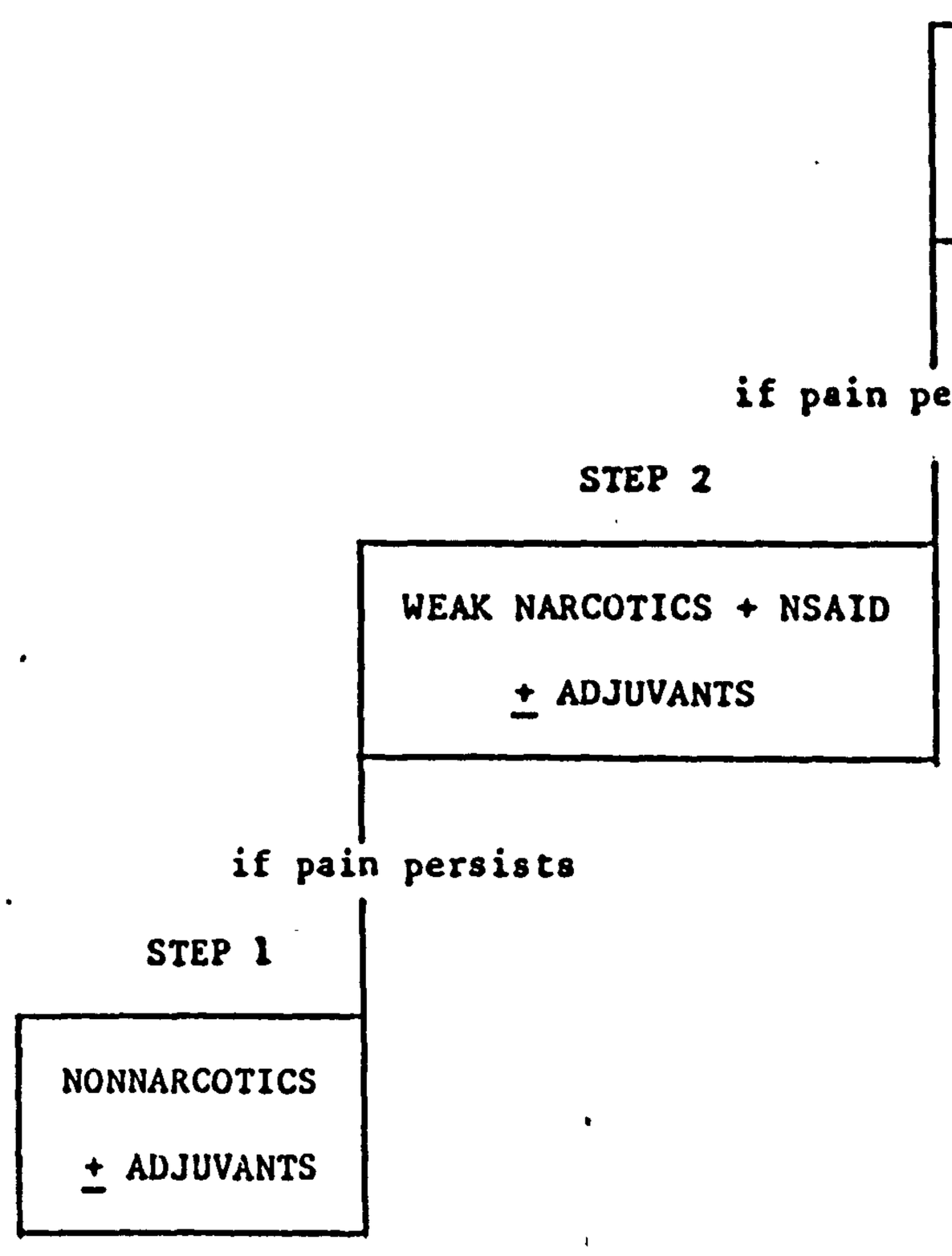
Table 1

A BASIC DRUG LIST

Category	Parent drug	Alternatives
1. Nonnarcotic	aspirin and other antirheumatics	paracetamol (acetominophen)
2. Weak narcotic	codeine	dextropropoxyphene
3. Strong narcotic	morphine	methadone pethidine (meperidine) buprenorphine standardized opium hydromorphone levorphanol
4. Adjuvant		
a. Anticonvulsants	carbamazepine	phenytoin
b. Psychotropics	chlorpromazine	prochlorperazine
	haloperidol	
	diazepam	
c. Antihistamines	hydroxyzine	
d. Antidepressants	amitryptiline	
e. Steroids	prednisolone	dexamethadone medroxyprogesterone

Figure 1

ANALGESIC LADDER IN CANCER PAIN RELIEF



N. NARC = aspirin - paracetamol and other antirheumatics

W. NARC. = codeine dextropropoxyphene

S. NARC. = morphine methadone

ADJ. = steroids - psychotropics (anxiolitics, antidepressants anticonvulsants)

STUDY DESIGN

The Guidelines Field Testing Protocol Study 2 will consist of three phases.

Phase I involves identifying the participating centres and study coordinators who will be responsible for local testing of the guidelines. These centre coordinators will complete the questionnaire described in Phase II, and submit it to the Collaborating Centre in Milan. The centre coordinator will also instruct local staff in the use of the guidelines document and will be responsible for monitoring patients and completing data forms for Phase III of the field testing trial.

In Phase II, a Participating Centre Questionnaire will be completed by the study coordinator for each participating centre. This questionnaire will request information about the availability of drugs for pain relief, the use of non-pharmacological methods for pain treatment, and the personnel resources, facilities, and continuing care networks which are available. Information about specific drugs to be used at each of the three steps of the ladder will also be obtained. This information is required to determine current feasibility for using the WHO Guidelines worldwide.

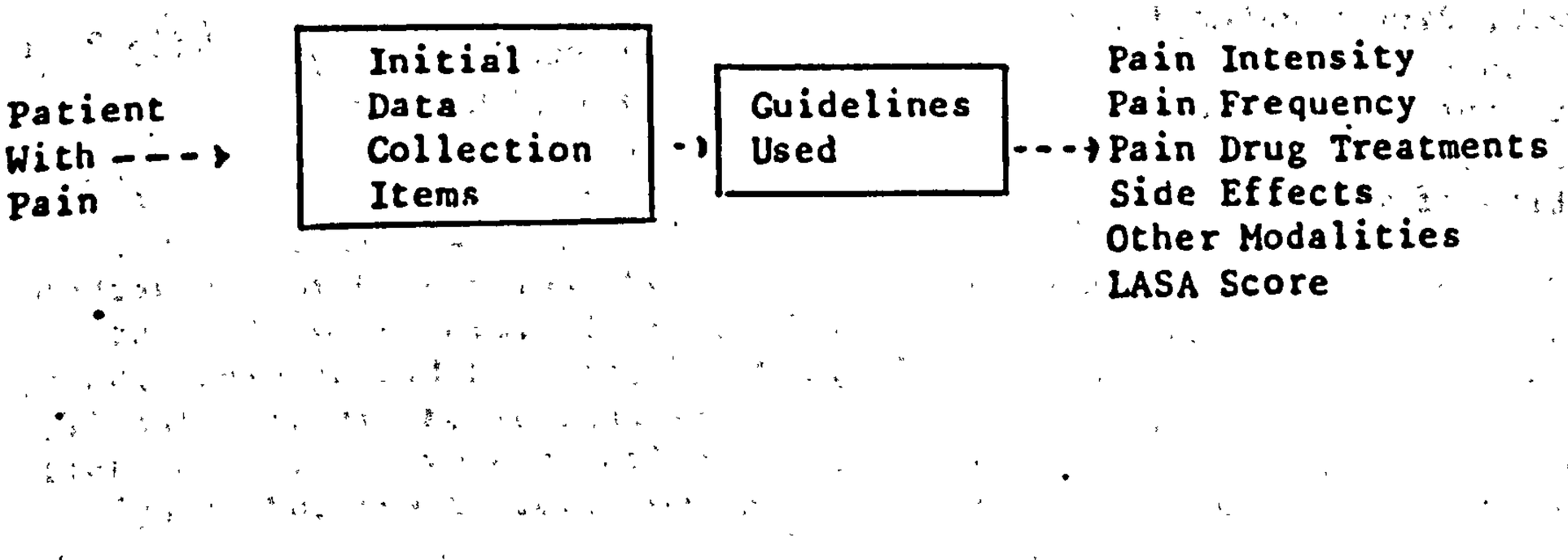
The evaluation of endpoints in Phase II will provide a description of the clinical settings which make up the sample of centres participating in the Guidelines Testing. It is required to obtain data on the feasibility for each clinic to apply the full guidelines procedures.

Not all clinics participating in the guidelines testing must have access to all of the drugs required for each level of the analgesic ladder. In some clinics where access to narcotic agents is limited, the ladder may only be feasible to apply up to step two. By evaluating results of Phase III according to the ability of the individual clinics to completely apply the guidelines we will obtain information about the possible role played by guidelines feasibility.

In Phase III, the guidelines will be applied for the treatment of pain in approximately 60 patients per participating centre. Initial baseline data on the status of the disease and the severity of the pain will be collected for each patient. The guidelines will be applied with monitoring of pain drug treatment and compliance with the analgesic ladder approach. Pain intensity, pain frequency, treatments, side effects, and use of other modalities will be recorded on follow-up forms. A LASA (linear analogue self-assessment) will also be used to obtain the patient's evaluation of the extent of relief achieved. The objectives for Phase III are to determine the level of compliance in delivery of guideline treatment and to determine the effectiveness for reducing pain intensity and frequency without side effects.

STUDY SCHEMA

Phase I – Identify participating centres and study coordinators.
Phase II – Centre questionnaires submitted by participating centres.
Phase III – Treat 60 patients on the guidelines approach to determine a) compliance, and b) effectiveness for reducing pain intensity without side effects. The first 10 patients from each centre will be considered pilot patients for the analysis.



Follow-up Report Schedule: Weekly for the first two weeks until stabilization of the drug regimen, thereafter, at each change in the pain drug treatment, weekly for two weeks after the change, and once every four weeks if stable.

6. STUDY OBJECTIVES

6.1 To determine the feasibility of using the WHO Guidelines in selected participating clinics.

6.2 To test the compliance with the WHO Guidelines approach in selected clinics.

6.3 To test the effectiveness of the WHO Guidelines in individual patients based on measurement of pain reduction with minimal side effects.

7. METHODS OF APPROACH (PHASE III)

Patients with cancer pain are to be identified and an initial interview form is to be completed. Following a complete history and physical to assess the causes of the pain, treatment for the pain is started according to the analgesic ladder. Follow-up forms are submitted to report on the level of pain and treatment modifications over time. Specific criteria for patient population, starting the ladder, forms submission and follow-up schedule, evaluation, and statistical considerations are presented below.

7.1 Patient Population - Patients with cancer pain are eligible for the study. Patient who received prior drug treatment for pain are eligible for the study and will begi the analgesic ladder at a step which depends on the prior treatment received.

7.2 Treatment Programme - When appropriate, the initial study treatment should be at Step 1 for at least three days regardless of the initial severity of the pain. Ste 1 when delivered according to the guidelines, may be effective even for severe pain. The initial entry step is described in the following table:

TABLE FOR DETERMINING INITIAL LADDER TREATMENT

Prior Drug Treatment Status		Initial Ladder Treatment
No prior drug treatment for pain	→	Start on Guidelines Step 1 for at least three days
Received prior drug treatment for pain but this prior treatment was not given according to the guidelines (e.g. only occasionally, not by the clock, at inadequate doses)	→	Start on Guidelines Step 1 for at least three days
Received prior drug treatment for pain which satisfies the requirements for Guidelines Step 1	→	Start on Guidelines Step 2 for at least three days
Received prior drug treatment for pain which satisfies the requirements for Guidelines Step 2 or 3 (i.e. regular administration of weak or strong narcotics)	→	Start on Guidelines Step 2 or 3 as appropriate

As described in the guidelines document, if pain persists or recurs, modification of the treatment, including stepping up the ladder, is to be made.

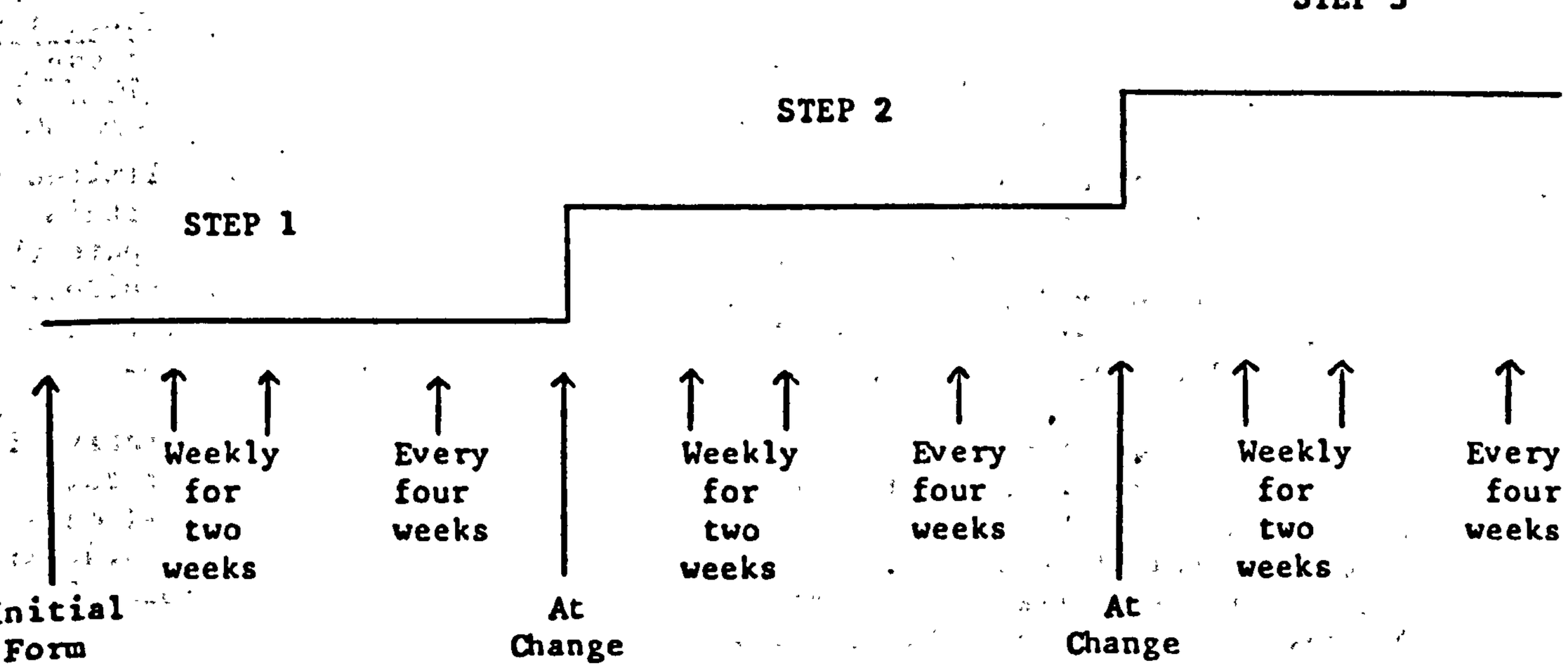
7.3 Forms Submission and Follow-up Schedule

A) The initial interview form is to be completed at the time of the first patient interview prior to beginning guidelines treatment. The purpose is to establish baseline data on the patient and his/her pain status at the time of starting the guidelines. A copy of this form is to be sent to the WHO Collaborating Centre in Milan as soon as it is completed to officially register the patient in the study.

B) Follow-up data are recorded on follow-up forms according to the schedule:

- Weekly assessements for the first two weeks to monitor stabilization of the initial ladder regimen.
- Every four weeks thereafter as a minimum contact if stable.
- At the time of change in the pain drug treatment.
- Weekly for two weeks after each change to monitor effect, and
- Every four weeks thereafter.

The diagram below illustrates the typical follow-up schedule:



Up to four follow-up reports can be made on each follow-up form. When each form is completed, a copy is to be sent to the WHO Collaborating Centre in Milan.

The critical evaluation of the effectiveness of the guidelines will be based upon the patient's self-assessment of pain and the degree of pain relief provided by the given treatment. A Patient's Current Self-Assessment of Pain Form is completed by the patient at each follow-up report. The results from this self-assessment are then recorded on the follow-up form.

Application of the guidelines and follow-up of the patients continues until death (or until the time of the final analysis of the results).

7.4 Other Pain Relief Modalities - The use of non-pharmacologic pain relief modalities is discouraged during the period of testing of the guidelines. If, however, the use of other modalities is felt to be in the best interest of the patient (i.e. radiation for bone pain) then these non-pharmacological treatments must be recorded on the Follow-up form. If traditional remedies (herbs, spells, etc.) are also being used, these should be noted but will not be grounds for disqualifying a patient. All patients are to be followed until death; those who receive non-guidelines pain treatment will have the influence of these interventions accounted for in the analysis, but are to continue to have guidelines treatment applied as appropriate.

7.5 Evaluation - The evaluation of analgesic effectiveness will be based on the patient's self report of pain intensity according to the four-point scale of none, slight, moderate, severe. The patient will be asked to specify the number of hour of pain, and the number of hours of sleep experienced (per 24 hours average). The simplified measures were adopted so that the field testing could be accomplished i a wide diversity of clinical settings. Reduction in the pain intensity report without intolerable side effects is the objective of the programme.

The experience of pain is subjective, and attempts to objectively quantify pa intensity may not adequately reflect the patient's overall impression about the effectiveness of the treatment. How the patient feels about the experience may be the most appropriate way to evaluate the programme. A linear analogue self-assessment (LASA) will be given to the patient to record how he/she evaluates the relief of pain provided by the given treatment [from "of no value" to "complet relief" on a 100 millimetre scale]. Each ladder step will be evaluated by LASA reports, and correlations between the LASA score and "objective" reports of pain intensity and hours will be obtained.

The duration of effect at each step of the ladder will be evaluated. Furthermore, the compliance with respect to providing stronger relief in response loss of analgesic effect at the previous level will be ascertained. Thus, it is critical that all modifications of pain treatment and the reasons for these modifications be recorded on the follow-up form.

7.6 Statistical Considerations - The objectives of the present study are limited to those described earlier: feasibility, compliance, and effectiveness within individual patients. No attempt is being made in this protocol to compare the guidelines with current practice, or to determine if introducing the guidelines ha an impact on the general quality of life for cancer patients with pain. The latte questions will be addressed by other protocols which are being planned.

Because the questions of interest in this protocol are not comparative in nature, we will use the concept of acceptable standard error estimates for evaluating extent of compliance to guidelines as a percent of the total cases entered. We would like to evaluate n patients per centre so that the standard err of the compliance estimate is no more than .06. If compliance is around 80%, then n=50 patients will satisfy this objective.

In terms of pain relief, 50 evaluable patients per centre will be sufficient t determine if patients on the guidelines experience a noticeable decrease in pain of one score or more. Indeed, a shift of one score or more can be detected with 95% probability using a two-sided alpha =.05 Wilcoxon Rank Sum Test based on 50 patient

A pilot study of 10 patients will be carried out in each centre. The Collaborating Centre will contact each participant after this pilot phase to clari guidelines compliance and data collection issues which arise. Thus, a total of 60 patients entered per centre are recommended for study.

REFERENCES

Daut, R.L., Cleeland, C.S., and Flanery, R.C. Development of the Wisconsin brief pain questionnaire to assess pain in cancer and other diseases, Pain, 17: 197-210, 1983.

Houde, R.W. Methods for measuring clinical pain in humans. Acta anaesth. scand. suppl, 74: 25-29, 1982.

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Sverdlow, M, and Stjernswärd, J: Cancer pain relief - an urgent problem, World Heath Forum, 3(3): 325-330, 1982.

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INSTRUCTIONS FOR COMPLETING THE WHO CANCER PAIN RELIEF GUIDELINES FIELD TESTING STUDY FORMS

The forms packet contains an Initial Interview Form, and three pages to record up to 12 follow-up reports. Patient's Current Self-Assessment of Pain Forms and additional follow-up forms are also provided.

Complete the first page of the initial interview when a patient with cancer pain is identified for the protocol. Submit a copy of the Initial Interview Form to the Collaborating Centre in Milan immediately to register the patient. Cases should be assigned numbers sequentially at each hospital. The hospital code and case number will serve to identify the patient on future forms.

- The form should be completed by an adequately instructed nurse.
- The patient's self-assessment of the level of pain and the degree of relief will be the principal items for evaluation.
- The items which should be completed at first visit are on the front page. In the other three pages up to 12 follow-ups can be registered.
- All dates are in day/month/year format.

FIRST VISIT

Report the following items:

Date of first visit (day, month, year), hospital name (with code number), patient's name and surname, sequentially determined case number for the patient, age, sex, height, weight, type of cancer classified according to organ pathology (i.e. breast, lung, colon-rectum etc.), and how many months since cancer was first diagnosed.

I PATIENT'S GENERAL CONDITION: indicate with a check (✓) if cancer is primary, disseminated or if state is now known. Indicate also if the patient is in terminal phase (i.e. prognosis of less than three months survival). Give the ECOG Performance Status Score according to the scale given on the pages of codes. State whether the patient is being treated as an inpatient or outpatient.

II DESCRIPTION OF PAIN: determine how long the patient has had cancer pain, in which part of the body the pain is localized, and what the present pain relates to. Using the Patient's Current Self-Assessment of Pain ask the patient to specify the mean intensity of pain felt in the past 48 hours (as a time-frame). Pain intensity is registered making use of three adjectives: slight, moderate and severe. The patient should then be asked the number of hours with pain per 24 hours (average), and the number of hours of sleep per 24 hours (average).

III PRESENT DRUG TREATMENT FOR PAIN: report the drug treatment for cancer pain relief which the patient is already undergoing. If no treatment is being given, check the box labelled "no drug treatment". If the patient is being treated pharmacologically, give the name of the drugs, the route (OR = oral route, IV = intravenous, IM = intramuscular, R = rectal), dose (mg), schedule and date started.

IV PAIN DRUG RELATED SIDE EFFECTS: in case the patient has already started pharmacological treatments for pain relief, report side effects, if any. If side effects occur, indicate 1 if intensity is slight; 2 if moderate; or 3 if severe, according to patient's judgement.

V OTHER PAIN RELIEVING MODALITIES: indicate the types of other treatments for pain relief undergone recently (within the past four weeks) by the patient, together with the date when treatment was started.

I INITIAL GUIDELINES TREATMENT: indicate by a check (✓) which of the four categories to efine the initial treatment step apply for this patient. (Note that patients receiving egular administration of weak or strong narcotics are not eligible for this field testing tudy, and that other patients should start treatment on Step 1 or Step 2 regardless of eported pain intensity.)

OLLOW UP REPORTING

A follow-up report is to be made:

- Weekly for the first two weeks to monitor stabilization of pain status.
- At any time the pain drug treatment is modified.
- Weekly for two weeks after any pain drug treatment modification to monitor the impact of the modification.
- And at a minimum of every four weeks thereafter for stable patients.

Each follow-up report refers to the period between the previous report and the current llow-up visit.

ATIENT'S CURRENT SELF-ASSESSMENT OF PAIN FORM:

At each follow-up assessment, the patient is to complete this form to provide an valuation of pain intensity, hours of pain, hours of sleep, and evaluation of pain relief rovided by the given treatment. This form may be used at a clinic visit or may be submitted or mailed) later to the clinic coordinator (registrar). Patients may provide elf-assessments without being required to return to the clinic.

OLLOW-UP FORM

DATE OF FOLLOW-UP REPORT: carefully and accurately enter the date of the evaluation as y/month/year.

ASK THE PATIENT(using the Self-Assessment Form): how bad is the pain? Mark with a eck (✓) the adjective which the patient uses to best explain the pain intensity felt. Give e number of hours per 24 hours (average) the patient had pain, and how many hours the tient slept per 24 hours (average). Using a measuring ruler (in millimetres), determine e LASA PAIN RELIEF SCORE (a number from 0 to 100 millimetres measuring from the left to the ght) indicated by the placement of the mark (x) by the patient on the LASA scale.

PAIN DRUG TREATMENT GIVEN SINCE THE PREVIOUS REPORT: indicate the drugs given, the ute of administration (OR = oral route, IV = intravenous, IM = intramuscular, R = rectal), e dose and schedule.

PAIN DRUG MODIFICATION: indicate the reason for any change in pharmacolgical treatment due to insufficient analgesic effect, excessive side effects, or other reasons (e.g. tient's lack of confidence in the drug, too expensive, etc).

PAIN DRUG RELATED SIDE EFFECTS: report side effects (1 = slight, 2 = moderate, 3 = vere) due to pharmacological treatment for pain relief.

OTHER PAIN RELIEVING MODALITIES: indicate any other treatment for pain relief which the tient underwent since the previous follow-up report.

PATIENT STATUS: indicate if the patient is alive, dead, or lost to follow-up and give e date. This question needs to be completed only once on each follow-up form. An dication that the patient has died signals the conclusion of follow-up, so that no more ta will be requested.

8. COMMENTS: enter any comments about the patient's pain and pain treatment course which might be helpful for evaluating the compliance and effectiveness of the guidelines for this patient.

DATA SUBMISSION

Patients are to be followed until death (or until the time when final data analysis for the study will begin). The initial interview data form and the follow-up forms containing data for 12 follow-up assessments should be submitted to the Collaborating Centre in Milan as soon as they are completed. Patient's Current Self-Assessment of Pain Forms need not be submitted, as the data from these forms will be transcribed onto the follow-up forms. Additional follow-up forms, each containing four possible follow-up visit reports, should be submitted to Milan when completed.

PILOT STUDY

The first 10 patients entered from each participating centre will be reviewed as a pilot study. Patient Self-Assessment Forms should be submitted to Milan for these patients to ensure the effectiveness of the methodology. Data for these patients should be submitted more frequently to faciliate rapid review and feedback from the Collaborating Centre in Milan.

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCORE

Score value that the patient is "capable" of performing

0 Normal Activity.

1 Symptoms but nearly fully ambulatory.

2 Some bed time, but needs to be in bed less than 50 per cent of the normal daytime.

3. Needs to be in bed greater than 50 per cent of normal daytime.

4. Unable to get out of bed.

OUTLINE OF APPROACH

Identify Participating Centres and Study Coordinators

GROUP 2

Those with Extensive Previous Exposure to The Guidelines

GROUP 1

Those without Extensive Previous Exposure to The Guidelines

STUDY 1

Baseline Data on Current Practice. Submit Initial Interview and Regular follow-up data on 30 cancer patients with pain

STUDY 2

Introduce Guidelines and Test Feasibility and Effectiveness. Submit initial interview and regular follow-up data on 10 pilot and 50 study cancer patients with pain treated using the guidelines principle

STUDY 3

Outreach Studies To be formulated

LASA INSTRUCTION EXAMPLE

PATIENT'S CURRENT SELF-ASSESSMENT OF PAIN

Patient's Name: _____ Date: _____

a. How bad is the pain? (past 48 hours)

none	☐	Please check one
slight	☐	
moderate	☐	
severe	☐	

b. How many hours do you have pain per 24 hours (average)? _____ hours

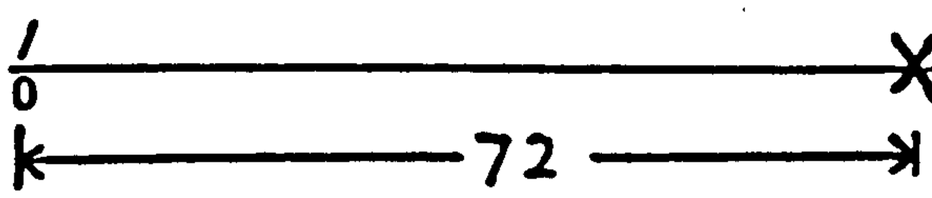
c. How many hours do you sleep per 24 hours (average)? _____ hours

d. Overall, how do you evaluate the relief of pain provided by the given treatment?

Please put a mark (x) on the scale below to show how you feel.

No Relief At All / 0 ——————————— 100 / Complete Pain Relief

Example:



Score: 72 millimetres written into follow-up form

STUDY 2

WHO PAIN RELIEF GUIDELINES FIELD TESTING STUDY 2
INITIAL INTERVIEW FORM

DATE ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ (d d m m y y)

HOSPITAL _____ ⌊_⌋⌊_⌋

PATIENT NAME _____

CASE NUMBER ⌊_⌋⌊_⌋⌊_⌋

AGE (Years) ⌊_⌋⌊_⌋ SEX ⌊_⌋

HEIGHT (cms) ⌊_⌋⌊_⌋⌊_⌋ WEIGHT (kg) ⌊_⌋⌊_⌋⌊_⌋

TYPE OF CANCER _____ ⌊_⌋⌊_⌋

HOW MANY MONTHS SINCE CANCER WAS DIAGNOSED? ⌊_⌋⌊_⌋ months

I PATIENT'S GENERAL CONDITION

STATE OF CANCER	Check
1. Primary only	☐
2. Disseminated	☐
3. Not known	☐

ECOG PERFORMANCE STATUS _____

Terminal patient (check if yes) ☐

HOSPITALIZATION STATUS	Check
1. In-patient	☐
2. Out-patient	☐
3. Home care only	☐

II DESCRIPTION OF PAIN

How long has the patient had the pain? ⌊_⌋⌊_⌋ months

Where is the pain? _____

Pain relates to (check each that applies):

☐ bone ☐ nerve compression ☐ soft-tissue extension ☐ Other: specify

☐ visceral involvement ☐ raised intracranial pressure ☐ muscle spasm _____

ASK THE PATIENT (PATIENT'S CURRENT SELF ASSESSMENT FORM):

a. How bad is the pain? (past 48 hours)

☐ none
☐ slight
☐ moderate
☐ severe

check one

b. How many hours of pain per 24 hours (average)? ⌊_⌋⌊_⌋ hours

c. How many hours of sleep per 24 hours (average)? ⌊_⌋⌊_⌋ hours

III PRESENT DRUG TREATMENT FOR PAIN – What drug is the patient taking for pain?

Check	Category	Generic name	route	dose	*schedule	date started
☐	No drug treatment					
☐	Non-narcotics					
☐	Weak narcotics					
☐	Strong narcotics					
☐	Anticonvulsants					
☐	Psychotropics					
☐	Antihistamines					
☐	Antidepressants					
☐	Steroids					
☐	Other					

* Schedule: Specify whether only occassionally (3 or less times per week), or frequently; as needed, or regularly by the clock.

IV PAIN DRUG RELATED SIDE EFFECTS (If present, give intensity: 0 = none; 1 = slight; 2 = moderate; 3 = severe)

☐ Nausea
☐ Vomiting
☐ Drowsiness
☐ Bleeding
☐ Gastralgia
☐ Restlessness
☐ Sweating
☐ Drymouth
☐ Tremor
☐ Vertigo
☐ Others (specify) _____

V OTHER PAIN RELIEVING MODALITIES (If yes, specify date and type)

Check		date (dd/mm/yy)	type
☐	Radiation		
☐	Surgery		
☐	Chemotherapy		
☐	Traditional Methods		
☐	Others (specify)		

VI INITIAL GUIDELINES TESTING – Indicate the initial guidelines step for this patient (check one which applies)

☐ No prior drug treatment for pain → Start on Guidelines Step 1 for at least 3 days

☐ Receiving prior drug treatment for pain, but this prior treatment was not given according to Guidelines (e.g. only occasionally (3 or less times per week) → Start on Guidelines Step 1 for at least 3 days

☐ Received prior drug treatment for pain which satisfied the requirements for Guidelines Step 1 → Start on Guidelines Step 2 for at least 3 days

☐ Received prior drug treatment for pain which satisfied the requirements for Guidelines Step 2 or 3 (i.e. regular administration of weak or strong narcotics) → Start of Guidelines Step 2 or 3 as indicated

STUDY

WHO PAIN RELIEF GUIDELINES FIELD TESTING STUDY 2 — PATIENT NAME _____

FOLLOW-UP EVALUATION DATA — HOSPITAL _____ ☐☐ — CASE NUMBER ☐☐

DATE OF FOLLOW-UP REPORT	☐☐ d ☐☐ m ☐☐ y	☐☐ d ☐☐ m ☐☐ y	☐☐ d ☐☐ m ☐☐ y	☐☐ d ☐☐ m ☐☐ y
ASK THE PATIENT: (Use self-assessment form)	check one	check one	check one	check one
a. How bad is the pain (past 48 hours)?	☐ none ☐ slight ☐ moderate ☐ severe	☐ none ☐ slight ☐ moderate ☐ severe	☐ none ☐ slight ☐ moderate ☐ severe	☐ none ☐ slight ☐ moderate ☐ severe
b. How many hours of pain per 24 hours (average)?	☐☐ hours	☐☐ hours	☐☐ hours	☐☐ hours
c. How many hours of sleep per 24 hours (average)?	☐☐ hours	☐☐ hours	☐☐ hours	☐☐ hours
d. LASA Pain Relief Score (0=none; 100=complete)	☐☐☐ millimetres	☐☐☐ millimetres	☐☐☐ millimetres	☐☐☐ millimetre
PAIN DRUG TREATMENT GIVEN SINCE THE PREVIOUS REPORT (give generic name, route [OR, IV, IM, R], dose and schedule	yes name/route/dose	yes name/route/dose	yes name/route/dose	yes name/route/dose
Step 1: Non-narcotics	☐	☐	☐	☐
Step 2: Weak narcotics	☐	☐	☐	☐
Step 3: Strong narcotics	☐	☐	☐	☐
ADJ Anticonvulsants	☐	☐	☐	☐
ADJ Psychotropics	☐	☐	☐	☐
ADJ Antihistamines	☐	☐	☐	☐
ADJ Antidepressants	☐	☐	☐	☐
ADJ Steroids	☐	☐	☐	☐
ADJ Others	☐	☐	☐	☐
PAIN DRUG MODIFICATION If pain drug is being modified, check reason(s):				
No analgesia	☐	☐	☐	☐
Side effects	☐	☐	☐	☐
Other (specify)	☐	☐	☐	☐
PAIN DRUG RELATED SIDE EFFECTS. Give intensity (0 = none; 1 = slight; 2 = moderate; 3 = severe)	intensity	intensity	intensity	intensity
Nausea	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐
Bleeding	☐	☐	☐	☐
Gastralgia	☐	☐	☐	☐
Restlessness	☐	☐	☐	☐
Sweating	☐	☐	☐	☐
Drymouth	☐	☐	☐	☐
Tremor	☐	☐	☐	☐
Vertigo	☐	☐	☐	☐
Others (specify)	☐	☐	☐	☐
" "	☐	☐	☐	☐
OTHER PAIN RELIEVING MODALITIES (If yes, specify date and type)	yes date type	yes date type	yes date type	yes date type
Radiation	☐	☐	☐	☐
Chemotherapy	☐	☐	☐	☐
Surgery	☐	☐	☐	☐
Traditional methods	☐	☐	☐	☐
Others (specify)	☐	☐	☐	☐

PATIENT STATUS

Alive	Yes ☐	Date last seen	☐☐ d ☐☐ m ☐☐ y
Dead	Yes ☐	Date of death	☐☐ d ☐☐ m ☐☐ y
Lost to follow-up	Yes ☐	Date lost to follow-up	☐☐ d ☐☐ m ☐☐ y

COMMENTS

PAGE NUMBERING AS FOUND IN THE ORIGINAL THESIS

Appendix 2

Patient self-completed assessment of pain relief

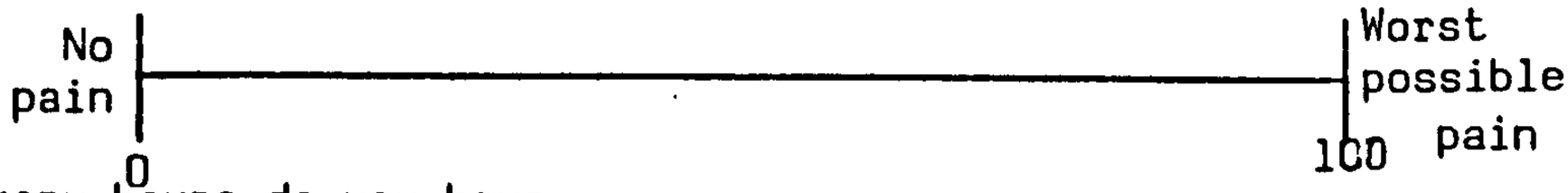
PATIENT'S CURRENT SELF-ASSESSMENT OF PAIN

Patient's Name: _____ Date: _____

a. How bad is the pain (past 48 hours)

none	☐	Please check one
slight	☐	
moderate	☐	
severe	☐	

b. Please put a mark (|) on the scale below to show how bad your worst pain has been (during the past 48 hours).



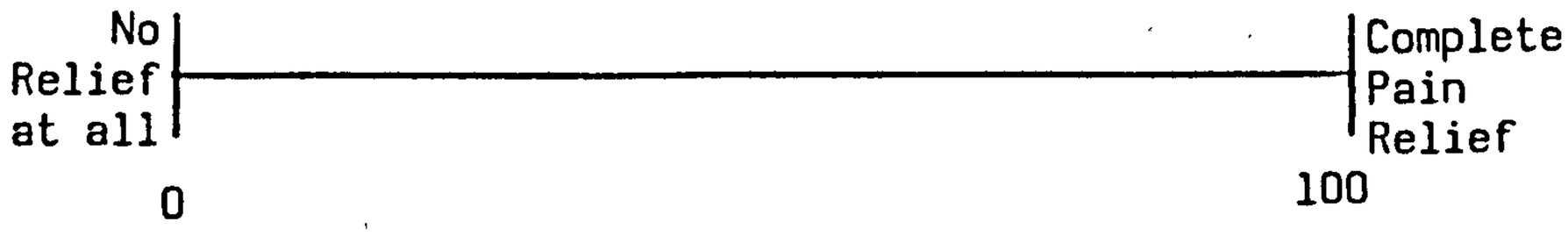
c. How many hours do you have pain per 24 hours (average)? _____ hours

d. How many hours do you sleep per 24 hours (average)? _____ hours

e. How is your pain compared with when you first started the current pain treatment?

much better	☐
better	☐
no change	☐
worse	☐

f. Please put a mark (|) on the scale below to show how much relief you now feel from your original pain.



Appendix 3

A survey of cancer pain control by South West England Palliative Care Teams

Patient Information Sheet

University of BRISTOL

A Survey of Pain Control in the South West

We (the Department of Palliative Medicine at the University of Bristol) would like you to help us with a research study we are carrying out in all palliative care departments in the South West of England. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
We are checking that the pain relief guidelines we currently follow are controlling cancer pain adequately in as many patients as possible. Previous research studies suggest that 8 out of 10 people with cancer pain will achieve adequate pain relief with these guidelines, but this has never been checked in the United Kingdom.

Why have I been chosen?
It would be impossible for us to involve everyone with cancer in the South West of England in our survey because of the large numbers involved. However, we can use a smaller number and still get accurate results, by asking a smaller "cross-section" of patients to complete the survey. We have decided to try to involve everyone seen by a palliative care team professional today.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are free to withdraw at any time. A decision not to take part or to withdraw will not affect your care at any time. We would be grateful if we could still record information such as your date of birth and diagnosis and level of activity, to ensure that we are not missing an important group of people from our survey.

What do I have to do?
If you agree to help us, we will ask you to fill in a questionnaire that will not be seen by the doctor or nurse managing your pain (this is

so that you can be as honest as you wish). This questionnaire should be placed in the attached envelope and the envelope then sealed. With your permission, they will also fill in a questionnaire about your cancer and your pain relief medication.

Will my taking part in this study be kept confidential?
We are not collecting your name on the questionnaire. However, we are collecting your postcode because this will allow us to see if social or financial factors have an impact on pain control. We will not use your postcode for any other purpose. It is possible that your identity could be revealed from your postcode but we will keep all questionnaires in locked filing cabinets and only the research team will have access to them. We will keep them for 15 years and then they will be confidentially destroyed. This is normal procedure for research records.
If you are completing this survey in your own home or in a day-care setting, with your permission we will send a letter to your general practitioner just to let them know that you have taken part in a pain survey.

What will happen to the results of the research study?
Once the study is completed, we will use the results to assess our current management of cancer pain and in particular to identify types of pain which may be more difficult to control. We will try to publish the results in a journal read by palliative care professionals. We will also send a copy of the results to all the centres that participated in the study.

Who is organising and funding the research?
This study is being conducted and funded by the Department of Palliative Medicine at the University of Bristol. It is one of a series of studies that I will submit in order to attain a higher degree (Doctor of Medicine).

Who has reviewed the study?
The South West Multi-centre Research Ethics Committee has approved this study
Thank you for your help.

Dr. Colette Reid
Research Fellow
0117 928 3336

Department of Palliative Medicine
University of Bristol

Appendix 4

A survey of cancer pain control by South West England Palliative Care Teams

Patient consent form

University of BRISTOL

Centre Number [ ]

Patient Identification Number for this trial [33 – 09]

CONSENT FORM

Title of Project: Cancer Pain Control in the South West

Name of Researcher: Dr. C Reid, Department of Palliative Medicine, University of Bristol.

Please initial box

1. I confirm that I have read and understand the information sheet dated 27/07/05 (V4) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care being affected. ☐

3. I agree to take part in the above study. ☐

4. I am happy for my palliative care doctor or nurse to fill in a questionnaire about my pain relief medication. ☐

5. I am happy for my GP to be informed of my participation (for patients seen in their own homes). ☐

6. I do not agree to take part in the above study, but agree to my date of birth, diagnosis and level of activity being recorded. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 5

A survey of cancer pain control by South West England Palliative Care Teams

Patient questionnaire

Pain Survey

Centre No. ☐

Study No 33 – 09

Q.1 How old are you? ☐☐ years

Q.2 What is your postcode? ☐☐☐☐☐☐☐

Q.3 Are you male ☐ 1 **or female** ☐ 2

Q.4 Do you have pain or need painkillers? Yes ☐ 1 No ☐ 2

If you have answered **no,** there are no more questions. Thank you for your help.

If you have answered **yes,** we would like to find out how bad your pain is.

Q.5 Please circle the number that best describes your pain **right now**

No pain **0 1 2 3 4 5 6 7 8 9 10** WORST pain imaginable

Q.6 Please circle the number that best describes your pain at its **worst** in the last week

No pain **0 1 2 3 4 5 6 7 8 9 10** WORST pain imaginable

Q.7 Please circle the number that best describes your pain at its **least** in the last week

No pain **0 1 2 3 4 5 6 7 8 9 10** WORST pain imaginable

Q.8 Please circle the number that best describes your pain **on average** in the last week

No pain **0 1 2 3 4 5 6 7 8 9 10** WORST pain imaginable

Q.9 Do you also experience temporary flares of pain that are worse than your usual pain?

Yes ☐ 1 No ☐ 2

Q.10 If yes, on average, how many times a day do you get these flares?

0-3 times per day ☐ 1 4-6 times per day ☐ 2

7-10 times per day ☐ 3 >10 times per day ☐ 4

Q.11 Do you take pain relief medication for these flares? (break-through or rescue doses) Yes ☐ 1 No ☐ 2

Q.12 If yes, does it work? Yes ☐ 1 No ☐ 2

Overall, is your pain controlled? Yes ☐ 1 No ☐ 2

Thank you

Appendix 6

A survey of cancer pain control by South West England Palliative Care Teams

Professional questionnaire

A survey of cancer pain control by South West England palliative care teams

Instructions for professionals

1. Please sign the professional's consent form and the site staff signature log at the beginning of the study day.

2. Please sign each patient's consent form.

3. Please fill in your professional number on all questionnaires. This is a combination of your initials and the last two digits of your year of birth. E.g. Mary Smith born in 1954 is MS54.

4. We recommend you fill in your questionnaire as the patient completes theirs. There are no patient details on the your professional questionnaire to identify which questionnaire belongs to which patient.

5. For patients seen in day care or community settings, please post a copy of the GP letter to the GP. Stamped envelopes are provided for this purpose.

6. Please make four copies of the signed patient consent form. One should be placed in the envelope along with both the patient and professional questionnaires, one in Section 10 of the Investigator Site File, one in the patient's notes and one copy is to be given to the patient when they are next seen.

7. At the end of the study each large envelope should contain a sealed patient questionnaire, the relevant professional questionnaire and a copy of the patient's consent form.

Please do not approach patients about the study if you are concerned it may add to their distress.

It is acceptable for you to help a patient complete their form if there is no-one accompanying them who could help.

THANK YOU for helping us with this pain survey.

Definitions

1. Opioid Switch

This is defined as a change of opioid. A change from morphine to diamorphine in a dying patient would be considered a switch and the reason would be "alternative route". However, changing from four-hourly morphine to modified-release morphine is a change of formulation and not an opioid switch.

Professional Questionnaire V2 18/07/05

Centre No. ☐ **Professional No.** ☐ **Patient No.** 33 – 09

Q.1 What is your role? (please tick box)

Doctor ☐ 1 Nurse ☐ 2

Q.2 In which setting are you seeing this patient?

Hospice IPU ☐ 1 Outpatient clinic ☐ 2

Day hospice ☐ 3 Home ☐ 4

Hospital ☐ 5

Q.3 Where is this patient's primary tumour(s)?

Breast ☐ 1 Prostate/ Genitourinary ☐ 6

Colorectal ☐ 2 Haematological ☐ 7

Lung ☐ 3 Mesothelioma ☐ 8

Upper GI ☐ 4 Head and neck ☐ 9

Unknown 1° ☐ 5 Other ☐ 10

Q.4 What is their ECOG performance status? ☐ (see below)

ECOG SCALE:

0 = Normal Activity
1 = Symptoms, but fully ambulatory
2 = Symptomatic but in bed <50% of the day
3 = Needs to be in bed >50% of the day but not bedridden
4 = Unable to get out of bed

Q.5 What do you think is the mechanism of their pain(s)?

Nociceptive ☐ 1 Neuropathic ☐ 2

Mixed ☐ 3 Other (e.g.tenesmus) ☐ 4

Q.5a If other please describe ☐

Q.5c If nociceptive, is the pain from

Bone ☐ 1

Soft tissue ☐ 2

Viscera ☐ 3

Q.6 Has this patient had radiotherapy for current pain control? Yes ☐ 1 No ☐ 2

Q.7 Has this patient had chemotherapy for current pain control? Yes ☐ 1 No ☐ 2

Q.8 Has this patient had a nerve block for current pain control? Yes ☐ 1 No ☐ 2

Q.9 Has this patient had spinal analgesia for current pain control? Yes ☐ 1 No ☐ 2

Q10. Which of the following is your patient currently using for pain control?

DRUG		**24 hour dose**	**Used for breakthrough pain?**	**Dose**
a) Aspirin	☐ 1		☐ 1	
b) Paracetamol	☐ 1		☐ 1	
c) NSAID	☐ 1		☐ 1	
d) COX2 Inhibitor	☐ 1		☐ 1	
e) Codeine	☐ 1		☐ 1	
f) Coproxamol	☐ 1		☐ 1	
g) Morphine	☐ 1		☐ 1	
h) Diamorphine	☐ 1		☐ 1	
i) Oxycodone	☐ 1		☐ 1	
j) Tramadol	☐ 1		☐ 1	
k) Hydromorphone	☐ 1		☐ 1	
l) Methadone	☐ 1		☐ 1	
m) Fentanyl	☐ 1		☐ 1	
n) Buprenorphine	☐ 1		☐ 1	

Q.11 What is the route of administration of the opioid?

PO ☐ 1 SC ☐ 2 IV ☐ 3

Intrathecal ☐ 4 Epidural ☐ 5 Transdermal ☐ 6

Please tick which drug is used for breakthrough pain. If none used please tick below

None used ☐ 1

Q12. Which of the following is your patient currently using for pain control? (Please tick appropriate boxes and give total 24 hour regular dose)

o) Steroid ☐ 1 Name ☐ Dose ☐

p) Anti-depressant ☐ 1 Name ☐ Dose ☐

q) Anti-convulsant ☐ 1 Name ☐ Dose ☐

r) Ketamine ☐ 1 Dose ☐ Breakthrough Dose ☐

s) Bisphosphonates ☐ PO ☐ 1 IV ☐ 2

t) Any other drugs or non-drug measure ☐ Please describe ☐

Q.13 Has this patient ever had an opioid switch?

Yes ☐ 1 No ☐ 2

Q.14 If yes, how many times? ☐

Q.15 What was the prime indication(s)?

Inadequate analgesia ☐ 1 Inadequate analgesia and side-effects ☐ 2

Alternative route (e.g. patch) ☐ 3 Adequate analgesia but side-effects ☐ 4

Poor adherence ☐ 5

Q.16 How long has this patient been known to the PCT?

Less than 24 hours ☐ 1 < 1 week ☐ 2 > 1 week ☐ 3

Any comments?

Date Completed ☐☐ ☐☐ 2005

Appendix 7

A survey of cancer pain control by South West England Palliative Care Teams

Letter of invitation to palliative care teams

«Title» «First_Name» «Surname»
«Role»
«Team_details»
«Address_1»
«Address_2»
«Address_3»
«Town»
«Postcode»

20 December 2004

Dear «Title» «Surname»

A Survey of Cancer Pain Control by South West England Palliative Care Teams

I am writing to ask if you would be prepared to participate in a survey of cancer pain control in a palliative care population. This survey aims to measure the prevalence of cancer pain, but also aims to estimate the effectiveness of the W.H.O. analgesic ladder by measuring the prevalence of uncontrolled cancer pain. We are assuming that patients being seen by palliative care professionals will have their pain managed according to the analgesic ladder. The W.H.O. studies conducted to validate the ladder suggested that about 80% of patients can have their pain controlled but this figure has not been supported by subsequent pain surveys from the United States and France. No similar studies have been carried out in the United Kingdom. The survey will also examine factors associated with poor pain control such as the nature of pains and breakthrough pain information.

I would like to conduct the survey from as many palliative care units as possible in the South West of England. My aim is to collect data from around 425 patients.

The survey will be conducted on one day only in a designated week and will involve both patients and professionals completing anonymised matched questionnaires. These have been kept as brief as possible. I am enclosing a copy of the questionnaires and the patient and professional information sheets, to give you an idea of the time involved.

At the moment I am in the process of submitting to the South West MREC but will also require R+D approval from each trust involved. In order to collect data from patients in community settings when seen by community palliative care nurses, we will need to have designated local investigators. (This would involve completing part C of the ethics application forms but should not be onerous.) If you would like to participate as a local investigator, or would like further information about the study, please return the enclosed reply form with your contact details and the name of your

trust. I aim to conduct the survey in March or April 2005 and would like to arrange an investigators' meeting for later in the year to discuss the study findings.

This study will contribute to my MD thesis based on the WHO analgesic ladder and the management of cancer pain. My supervisor is Professor Geoffrey Hanks at the University of Bristol.

Thank you for your time

Yours sincerely

Dr Colette Reid
Research Fellow

Appendix 8

A survey of cancer pain control by South West England Palliative Care Teams

Ethics application form

NHS Research Ethics Committee NHS

APPLICATION FORM

This form should be completed by the Chief Investigator, after reading the Guidance Notes.
See Glossary for clarification of different terms in the application form.

Short Title and version number: (maximum 70 characters – this will be inserted as header on all forms)
Cancer Pain Survey

Name of NHS Research Ethics Committee to which application for ethical review is being made:
SWMREC

Project Reference number from above REC: 05/MRE06/21

Submission Date: 08/02/2005

PART A: Introduction

A1. Title of Research

Full title: A Survey of Cancer Pain Control by South West England Palliative Care Teams

Key words: Cancer pain palliative care

A2. Chief Investigator

Title: Dr

Forename/Initials: Colette

Surname: Reid

Post: Research Fellow in Palliative Medicine

Qualifications: MBChB, MRCGP

Organisation: Department of Palliative Medicine, University of Bristol

Address: Level C, Bristol Haematology and Oncology Centre
Horfield Road
BRISTOL

Post Code: BS2 8ED

E-mail: Colette.reid@bristol.ac.uk

Telephone: 0117 928 3336

Fax: 0117 928 3865

...maximum 2 pages of A4 for each chief investigator associated with application

A3. Proposed Study Dates and Duration

Start Date: 01/05/2005

End Date: 31/05/2005

Duration: Months: 1 ; Years:

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☑ Publicly funded trial or scientific investigation
- ☑ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

A5. Tick the box if your research:

- ☐ Involves testing a medicinal product
- ☐ Involves investigating a medical device
- ☐ Involves additional radiation above that required for clinical care
- ☐ Involves using stored samples of human biological material (e.g. blood, tissue)
- ☐ Involves taking new samples of human biological material
- ☐ Involves only patient records or data, with no other direct patient contact
- ☐ Involves prisoners or others in custodial care
- ☐ Involves adults unable to consent for themselves through physical or mental incapacity
- ☐ Has the primary aim of being educational (e.g. a student project, or a project or research necessary for a postgraduate degree or diploma)

A6. Do you consider that this research falls within the category where there is no need to appoint a Principal Investigator at each site?

○ Yes ◉ No

If Yes, please justify:

Advice will be given under the category. Note: not to apply. Some studies do not require further consideration. Please see the issues of research ethics committee. Only the full committee approval to proceed from the host organisation.

PART A: Section 1

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

The principal research question is how effective is the World Health Organization (W.H.O.) analgesic ladder, as utilised by specialists in palliative care, in the management of cancer pain. This will be estimated by measuring the prevalence of uncontrolled cancer pain in a population of patients referred to specialist palliative care teams.

A8. What are the secondary research questions/objectives? *(If applicable, must be in language comprehensible to a lay person.)*

To define/identify in a population of patients referred to palliative care teams: 1. The point prevalence of cancer pain 2.The proportions of different types of cancer pain 3.Factors associated with poor pain control 4.The proportion of patients who need a change of opioid or an anaesthetic procedure and 5.Whether or not patients are receiving pain medication appropriate to their pain.

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance?*(Must be in language comprehensible to a lay person.)*

Pain is the most common symptom in patients referred to palliative care services. The W.H.O. analgesic ladder provides the framework for the treatment of cancer pain worldwide and was validated at its inception in 1986 by several studies coordinated by the W.H.O. These studies suggested that 80% of cancer pain could be controlled by appropriate use of the ladder. However two large pain prevalence studies conducted in France and U.S.A. in 1991 suggested that cancer pain control remained poor, inspite of widespread adoption of the principles of the ladder. A Scottish audit of cancer pain control conducted in 2000 also revealed poor pain control with almost 50% of patients recording a pain score of 4 or greater on a 0–10 scale. A systematic review of the validation studies, by Jadad and Browman, published in 1995, questioned the quality of the evidence supporting the ladder's effectiveness and called for further research. These data together suggest that the proportion of patients with unrelieved pain is possibly much higher than we believe. This study is part of a series of studies investigating the continuing utility and effectiveness of the ladder.

A10. Give a brief synopsis/summary of methods and overview of the planned research, including a brief explanation of the theoretical framework which informs it. It should include a brief description of how prospective research participants and concerned communities (not necessarily geographical) from which they are drawn have been consulted over the design and details of the research.
(Where appropriate a flow chart or diagram should be submitted separately. It should be clear exactly what will happen to the research participant, how many times and in what order).

This section MUST be completed in language comprehensible to the lay person. Do NOT simply reproduce the protocol.

This is a cross-sectional study. All patients seen on a single designated day by a doctor or nurse in a palliative care team will be asked if they wish to participate, provided they are competent and that in the opinion of the health professional their participation will not cause distress.
Those who are willing to participate will then be asked to complete a questionnaire, (one side of A4) which should not take more than 10 minutes to complete. The professional seeing the patient will also be asked to complete a questionnaire about that patient's treatment (two sides of A4). The questionnaires will be anonymised, but will have matching numbers to ensure paired data is obtained. Patients will be asked to score their pain on a 11 point numerical rating scale. This scale has been chosen because of its demonstrated utility in this population and because scores of 5 or greater on this scale have been shown to correspond to significant interference with function in patients.
We wish to obtain a representative group of palliative care patients and so need to recruit from all settings in which palliative care patients are seen by a health care professional. This means we will be recruiting from hospital wards and outpatients, hospice in-patient units and day centres and also recruiting patients seen by professionals in their own homes.
The questionnaires will be piloted in the investigator's institution. Feedback from both patients and professionals after this pilot will be used to amend the questionnaire design.

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

○ Yes ◉ No

A12. Will the research participants receive any clinical intervention(s) or procedure(s) including taking samples of human biological material over and above that which would normally be considered a part of routine clinical care?

○ Yes ◉ No

A13. Will the research participant be subject to any non–clinical research–related intervention(s) or procedure(s)? *(These include interviews, non–clinical observations and use of questionnaires.)*

◉ Yes ○ No

Additional Intervention	Average number per patient	Average time taken (mins/hours/days)	Details of additional intervention or procedure, who will undertake it, and what training they have received.
Other Questionnaire	1	10 minutes	The questionnaire will be handed to the patient by the palliative care professional, but will be completed independently by the patient where possible.

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

Question A14 below is not applicable if No is selected in question A13.

○ Yes ◉ No

The Information Sheet should make clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

10 minutes

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non–clinical)?

None

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

None

A18. What is the potential for benefit to research participants?

None

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves? *(if any)*

None

A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

We will ask that all patients seen as part of routine practice on a designated day will be considered for inclusion in the study. However, the decision to approach the patient will be at the discretion of the palliative care professional, to ensure that patients who are unable to provide consent or for whom the study may cause uneccessary distress are not approached. Potential participants will be given the patient information leaflet to read. In centres where it is feasible, this leaflet will be given to patients 24 hours before the designated data collection day. Patients who are willing to participate will then be asked for their written consent by the health professional.

A21. Where research participants will be recruited via advertisement, give specific details.

- ☑ Not Applicable

If applicable enclose a copy of the advertisement (radio script/website page) to be used. (With version number and date)

A22. What are the principal inclusion criteria? *(Please justify)*

All patients with cancer seen by a palliative care professional on a single designated day, who are able and willing to complete a pain questionnaire in order to calculate the prevalence of unrelieved pain in a representative sample.

A23. What are the principal exclusion criteria? *(Please justify)*

Patients unable or unwilling to complete a pain questionnaire.
Patients for whom the palliative care professional feels participation is inappropriate.

A24. Will the participants be from any of the following groups? *(Tick as appropriate)*

- ☐ Children under 16
- ☐ Adults with learning disabilities
- ☐ Adults who are unconscious or very severely ill
- ☑ Adults who have a terminal illness
- ☐ Adults in emergency situations
- ☐ Adults with mental illness (particularly if detained under Mental Health Legislation)
- ☐ Adults suffering from dementia
- ☐ Prisoners
- ☐ Young Offenders
- ☐ Adults in Scotland who are unable to consent for themselves
- ☐ Healthy Volunteers
- ☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- ☐ Other vulnerable groups

Justify their inclusion.
Pain is the commonest symptom of advanced cancer and causes great anxiety for patients and their families.

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

◉ Yes ○ No ○ Not Known

If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?
We are investigating the management of cancer pain so it is possible that some participants will have previously been involved in cancer treatment trials. However, this study will only require 10 minutes of the participant's time.

A26. Will informed consent be obtained from the research participants?

◉ Yes ○ No

If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe the arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.
The palliative care professional seeing the patient will inform that patient about the study and invite them to read the Patient Information Sheet. Those patients who are willing to participate will be asked for their written consent prior to completing the questionnaire.

Copies of the written information to be given to participants must accompany this application

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

If Yes, attach a copy of the information sheet and consent form as appropriate

A28. How long will the participant have to decide whether to take part in the research?

The time available to decide about participating will vary between settings. In in-patient units potential participants will be given information 24 hours before the designated data collection day. However, in the community setting, it is likely that participants will have to make a decision about participation within an hour.

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

We will use hospital translaters where possible and relatives if available.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Not applicable.

A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit? *(see Guidance Notes)*

○ Yes ◉ No

A32a. Will the research participants' General Practitioner be informed that they are taking part in the study?

○ Yes ◉ No

If Yes please enclose a copy of the information sheet/letter for the GP with version number and date

A32b. Will permission be sought from the research participants to inform their GP before this is done?

○ Yes ◉ No

If No to either question, explain why not
It is unlikely that such information will be useful for the General Practitioner.

If you have made explicit in the patient information sheet that research participants GP will be informed

A33. Will individual research participants receive any payments for taking part in this research?

○ Yes ◉ No

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

○ Yes ◉ No

A35. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for *negligent* harm?

I am attaching a letter from the University of Bristol outlining the liability insurance policy for this study

Please provide copies of the relevant documents

A36. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for *non-negligent* harm?

None (not applicable)

Please provide copies of the relevant documents

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☑ Written feedback to research participants
- ☐ Presentation to participants or relevant community groups
- ☐ Other/none e.g. Cochrane Review, University Library

A38. How will the results of research be made available to research participants and communities from which they are drawn?

The individual results for each team will be fed back to that team along with the pooled results for the whole group.

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- ☐ Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- ☐ Electronic transfer by magnetic or optical media, e-mail or computer networks
- ☐ Sharing of data with other organisations
- ☐ Export of data outside the European Union
- ☑ Use of personal addresses, postcodes, faxes, e-mails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal data on any of the following:
  - ☐ Manual files including X-rays
  - ☑ NHS computers
  - ☑ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:
We will use the participants' postcodes to examine any associations between pain control and socio-economic deprivation using Townsend Scores.
Data stored will be password protected on university computers.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:

The questionnaires will be anonymous. Each patient will be assigned a unique study identification number. Each professional will have an identification number derived from their initials and year of birth.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

Data analysis will take place in the Department of Palliative Medicine at the University of Bristol, by Dr Colette Reid.

A42. Who will have control of and act as the custodian for the data generated by the study?

Dr Colette Reid and Professor Geoffrey Hanks.

A43. Who will have access to the data generated by the study?

The Department of Palliative Medicine at the University of Bristol.

A44. For how long will data from the study be stored?

5 Years Months

Give details of where they will be stored, who will have access and the custodial arrangements for the data:
Paper questionnaires will be stored in locked filing cabinets. The information extracted will be stored in an Access database which will be password protected and accessed by the investigators only.

A45. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi–centre research group
- [x] Internal review (e.g. involving colleagues, academic supervisor)
- [ ] None external to the investigator
- [ ] Other, e.g. methodological guidelines

If you are not in possession of any referees or other scientific critique reports relevant to your proposed study, justify and describe the review process and outcome. If review has been undertaken but not seen by the researcher, give the details of the body which has undertaken the review:

A46. Has similar research on this topic been done before?

○ Yes ◉ No

A47. Have all existing sources of evidence, especially systematic reviews, been fully considered?

◉ Yes ○ No

If Yes, please give details of search strategy used. If No, explain why not.
Using a search strategy of cancer pain and prevalence, previous studies were identified. Whilst these have examined pain prevalence, the majority have not measured pain severity or attempted to estimate the efficacy of current pain management. In addition, much of this research has been conducted outside of the United Kingdom. No similar published studies have been conducted in palliative care settings in the United Kingdom.

A48. What is the primary outcome measure for the study?

The prevalence of uncontrolled cancer pain. (The percentage of patients with pain who record a pain score of >5 on a 0–10 numerical rating scale).

A49. What are the secondary outcome measures? *(if any)*

1. Prevalence of cancer pain 2. Use of analgesic medication and other pain treatments 3. Factors associated with pain that is difficult to control.

A50. How many participants will be recruited? How many of these participants will be in a control group?

425

A51. Has the size of the study been informed by a formal statistical power calculation?

◉ Yes ○ No

If Yes, indicate the basis upon which this was done, giving sufficient information to allow the replication of the calculation:
If the true proportion of controlled cancer pain is 80%, then 250 questionnaires from patients with pain will allow us to calculate this with 95% confidence intervals of 75–85%. It is likely that the overall pain prevalence is 65% and so allowing for 5% missing data and 20% failure to complete by the health professional, we will require 425 (250*1.35*1.05*1.2) patients overall.

A52. Has a statistician given an opinion about the statistical aspects of the research?

◉ Yes ○ No

If Yes, give the name and contact details:
Mrs R Greenwood, RDSU, Level 6 King Edward Building, Bristol Royal Infirmary, Marlborough Street, Bristol BS28HW

If Yes, give a brief summary of advice offered and attach a copy of comments if available:
Advice given about number of completed questionnaires required and also appropriate statistical tests to use when analysing the data.

If Yes, enclose a copy of the comments. If No, please enclose a summary of the opinion

A53. Describe the statistical methods and/or other relevant methodological approaches (e.g. for qualitative research) to be used in the analysis of the results. Give details of the methods of randomisation process to be used if applicable:

We will compare those patients with pain â€œon averageâ€ scores of <5 with those with pain â€œon averageâ€ scores of >5 using T-tests for continuous variables and chi-squared tests for categorical variables.
We will compare the associations of a numerical rating scale score of >5 for pain â€œon averageâ€ with the answer â€œNoâ€ for the question â€œOverall is your pain controlled?â€ using chi-squared tests.
We will investigate correlations between pain scores and age, performance status, and socio-economic status (using Townsend Deprivation scores), by employing a Spearmanâ€™s rank correlation coefficient as it is not thought that age will have a normal distribution.

A54. Where will the research take place? *(Tick as appropriate)*

☑ UK
☐ Other states in European Union
☐ Other countries in European Economic Area
☐ Other

Give details:
All palliative care teams in the South West of England, identified using the Hospice Directory 2004, have been contacted and asked if they wish to participate in the study. We have had positive responses from almost all. Each of these teams will be

visited by a research nurse prior to the designated data collection day.

A55. Has this or a similiar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?

○ Yes ◉ No

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

	Number of organisations
☑ Acute teaching NHS Trusts	7
☑ Acute NHS Trusts	8
☐ NHS Community and/or Primary Care Trusts	
☐ NHS Trusts providing Mental Healthcare	
☐ NHS Care Trusts	
☐ Social Care Organisations	
☐ Prisons	
☐ Independent hospitals	
☐ Educational establishments	
☐ Independent research units	
☑ Other (give details)	21

Other:
We hope to recruit from both independant hospices and palliative care units and NHS hospices and palliative care units.

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

Monitoring and auditing will be undertaken as part of the University of Bristol's routine monitoring/auditing programme. This study will be in the cohort of studies from which a routine sample will be taken and monitored and/or audited.

Will a data monitoring committee be convened?

○ Yes ◉ No

What are the criteria for electively stopping the trial or other research prematurely?

Not applicable.

A58. Has funding for research been secured?

◉ Yes ○ No

If Yes, give details of funding organisation(s) and amount secured and duration:

Organisation:	Napp Pharmaceuticals
Address:	Cambridge Science Park Milton Road CAMBRIDGE
Post Code:	CB4 0GW
UK contact:	
Telephone:	01223 424444 Fax:
E-mail:	
Amount (£):	3684.30 Duration: 1 Months

Organisation:	The Dr Mortimer and Theresa Sackler Foundation
Address:	67 Chester Square LONDON
Post Code:	SW1W 9DU
UK contact:	
Telephone:	Fax:
E-mail:	
Amount (£):	20990 Duration: 6 Months

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

○ Yes ◉ No ○ Not Known

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

◉ Yes ○ No ○ Not Known

Give details of the organisation which will act as the sponsor of the research:

UK contact:

Title:			
Forename/Initials:	Gillian		
Surname:	Tallents		
Organisation:	The University of Bristol		
Address:	University of Bristol, 3rd Floor, Senate House, Tyndall Avenue Bristol	Telephone:	0117 928 8676
		Fax:	0117 929 8383
Postcode:	BS8 1TH		
E-mail:	gillian.tallents@bristol.ac.uk		

A60. Has any responsibility for the research been delegated to a subcontractor?

○ Yes ◉ No

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

○ Yes ◉ No

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

○ Yes ◉ No

A64. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share-holding, personal relationship etc.) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

A65. Other relevant reference numbers if known*(give details and version numbers as appropriate):*

Applicant's/organisation's own reference number, e.g. RD(if available):
Sponsor's/protocol number:
Funder's reference number:
International Standard Randomised Controlled Trial Number (ISRCTN):
European Clinical Trials Database (EudraCT) number:
Project website:

A66. Other key investigators/collaborators*(all grant co-applicants should be listed)*

Title:	Professor	
	Forename/Initials: Geoffrey	Surname: Hanks
Post:	Professor of Palliative Medicine	
Qualifications:	DSc BSc MB FRCP FRCPE FFPM	
Organisation:	University of Bristol	
Address:	Level C	
	Bristol Haematology and Oncology Centre	Telephone: 0117 928 3336
	Horfield Road, BRISTOL	Fax: 0117 928 3865
Postcode:	BS2 8ED	
E-mail:	debbie.ashby@bristol.ac.uk	

A67. If the research involves a specific intervention, (e.g. a drug, medical device, dietary manipulation, lifestyle change etc.), what arrangements are being made for continued provision of this for the participant (if appropriate) once the research has finished?

☑ Not Applicable

PART A: Summary of Ethical Issues

A68. What do you consider to be the main ethical issues or problems which may arise with the proposed study and what steps will be taken to address these?

The main ethical issue is that the health professional inviting a patient to take part in the study will in some cases be the patient's usual palliative care professional. We will inform all health professionals that no patient should feel obliged to participate and that all patients must understand that not doing so will not affect their care in any way.

A69. Do you need to add further information about certain questions in Part A?

This question is not applicable for the online version of COREC form.

PART B: Section 7 – Declaration

– The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

– I undertake to abide by the ethical principals underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

– If the research is approved I undertake to adhere without unagreed deviation to the study protocol, the terms of the full application of which the main REC has given a favourable and any conditions set out by the main REC in giving its favourable opinion.

– I undertake to inform the main REC of any changes in the protocol, and to submit annual reports setting out the progress of the research.

– I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.

– I understand that research records/data may be subject to inspection for audit purposes if required in future.

– I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.

Signature: .....

Date: (dd/mm/yyyy)

Print Name:

1. Do you need to add further information about certain questions in part B?

This question is not applicable for the online version of COREC form.

ENSURE THAT YOU COMPLETE AND SIGN THE FORM AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS

PART C: Site-Specific Assessment (SSA)

This form should be completed by the Principal Investigator for each site (see glossary)

[redacted]

[redacted]

Name of NHS Research Ethics Committee to which application for ethical review is being made:
SWMREC
Project Reference number from above REC: 05/MRE06/21

Name of NHS REC responsible for SSA:
Central and South Bristol Research Ethics Committee.
SSA reference (for REC office use only):

Questions C1, C4, C5, C6, C7, C8 and C13a correspond to questions A1, A2, A65, A10, A12, A13 and A29 on main application form respectively and will populate automatically:

C1. Title of Research *(Populated from A1)*

Full title: A Survey of Cancer Pain Control by South West England Palliative Care Teams
Key words: Cancer pain palliative care

C2. Who is the Principal Investigator for this study at this site?

Title: Dr Forename/Initials: Colette Surname: Reid

Post: Research Fellow in Palliative Medicine
Qualifications: MBChB, MRCGP
Organisation: Department of Palliative Medicine
Address: Level C BHOC
Horfield Road
BRISTOL
Post Code: BS2 8ED
E-mail: Colette.reid@bristol.ac.uk
Telephone: 0117 928 4591
Fax: 0117 928 3865

[redacted]

C3. Indicate the number of trials/projects within the organisation that the local Principal Investigator has been involved with in the previous 12 months: 2

How many are still current (active or recruiting)? 2

Give details of other members of the local research team responsible to the local Principal Investigator

Title: Mrs
Forename/Initials: Tina
Surname: Quinn
Position: Clinical Nurse Specialist
Qualifications:
Role in the research team: Research Nurse

[illegible]

C4. Chief Investigator *(Populated from A2)*

Title: Dr Forename/Initials: Colette Surname: Reid
Post: Research Fellow in Palliative Medicine
Qualifications: MBChB, MRCGP
Organisation: Department of Palliative Medicine, University of Bristol
Address: Level C, Bristol Haematology and Oncology Centre
Horfield Road
BRISTOL
Post Code: BS2 8ED
E-mail: Colette.reid@bristol.ac.uk
Telephone: 0117 928 3336
Fax: 0117 928 3865

[illegible]

C5. Other relevant reference numbers If known *(Populated from A65)*

Applicants/organisation's own reference number, e.g. RD(if available):
Sponsor's/protocol number:
Funder's reference number:
International Standard Randomized Controlled Trial Number (ISRCTN):
European Clinical Trials Database (EudraCT) Number:
Project website:

C6. Give a brief synopsis/summary of methods and overview of the planned research. This should include a brief description of how prospective research participants and concerned communities (not necessarily geographical) from which they are drawn have been consulted over the design and details of the research?
(Where appropriate a flow chart or diagram should be submitted separately. It should be clear exactly what will happen to the research participant, how many times and in what order). (Populated from A10)

This is a cross-sectional study. All patients seen on a single designated day by a doctor or nurse in a palliative care team will be asked if they wish to participate, provided they are competent and that in the opinion of the health professional their participation will not cause distress.
Those who are willing to participate will then be asked to complete a questionnaire, (one side of A4) which should not take more than 10 minutes to complete. The professional seeing the patient will also be asked to complete a questionnaire about that patient's treatment (two sides of A4). The questionnaires will be anonymised, but will have matching numbers to ensure paired data is obtained. Patients will be asked to score their pain on a 11 point numerical rating scale. This scale has been chosen because of its demonstrated utility in this population and because scores of 5 or greater on this scale have been shown to correspond to significant interference with function in patients.

We wish to obtain a representative group of palliative care patients and so need to recruit from all settings in which palliative care patients are seen by a health care professional. This means we will be recruiting from hospital wards and outpatients, hospice in–patient units and day centres and also recruiting patients seen by professionals in their own homes.
The questionnaires will be piloted in the investigator's institution. Feedback from both patients and professionals after this pilot will be used to amend the questionnaire design.

C7. Will the research participants receive any clinical intervention(s) or procedure(s) including taking samples of human biological material over and above that which would normally be considered a part of routine clinical care? *(Populated from A12)*

○ Yes ◉ No

C8. Will the research participant be subject to any non–clinical research–related intervention(s) or procedure(s)? *(These include interviews, non–clinical observations and use of questionnaires.)(Populated from A13)*

◉ Yes ○ No

Additional Intervention	Average number per patient	Average time taken (mins/hours/days)	Details of additional intervention or procedure, who will undertake it, and what training they have received.
Other Questionnaire	1	10 minutes	The questionnaire will be handed to the patient by the palliative care professional, but will be completed independently by the patient where possible.

C9a. Give the name of the NHS or other organisation with which the PI holds the necessary contract (substantive or honorary) to undertake the research at this site:

United Bristol Healthcare Trust

C9b. Give the name of the research site for which the PI is responsible, if different from the above. (The site may be a whole organisation, an individual unit, or a consortium):

C9c. Give the name and contact details for the Research Governance lead for the research site:

Title:
Forename/Initials:
Surname:
Address:

Telephone:
Fax:

Postcode:
E–mail:

C10. Specify the location(s)/department(s) within the NHS or other organisation where the research will take place.

Patients will be recruited from both in–patient and outpatient settings in the Haematology and Oncology Centre and throughout the Bristol Royal Infirmary.

C11. How many research participants/samples is it anticipated will be recruited/obtained from this organisation in total?

All patients seen by the Hospital Palliative Care Team on a single designated day will be eligible to participate. This will be 10–20 patients.

C12a. Give details of who will be responsible for obtaining informed consent locally, their qualifications and relevant expertise and training in obtaining consent for research purposes:

C13a. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.) (Populated from A29)*

We will use hospital translaters where possible and relatives if available.

C13b. What local arrangements have been made to meet these requirements (where applicable)?

C14. In addition to informing the GP (if required), what arrangements have been made to inform those responsible for the care of the research participants in the host care organisation of their involvement in the research?

A copy of the patient's signed consent form and the Professional Information Sheet will be placed in the patient's notes.

C15. Are the facilities and staffing available locally adequate to perform any necessary procedures or interventions required for the study, and to deal with any unforseen consequences of these? *(This should include consideration of procedures and interventions in both control and intervention arms of a study.)*

◉ Yes ○ No

If Yes, give the information necessary to justify your answer. If No, indicate what arrangements are being made to deal with the situation:

C16a. Give brief details of a contact point where participants may obtain further information about the study.

The Department of Palliative Medicine in the Bristol Haematology and Oncology Centre.

16b. What is the contact point for potential complaints by research participants?

16c. Is there a local source where potential participants can obtain independent information about being involved in a research study?

16d. Please specify the headed paper to be used for the participant information sheet?

The University of bristol headed paper will be used in all centres.

C17. If any extra support might be required by research participants as a result of their participation, what local arrangements are being made to provide this?

not applicable

C18. Do you need to add further information about certain questions in Part C?

This question is not applicable for the online version of COREC form.

PART C: Declaration

– The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

– I undertake to abide by the ethical principles underpinning the Declaration of Helsinki and good practice guidelines on current proper conduct or research.

– If the research is approved I undertake to adhere without unagreed deviation to the study protocol, the terms of the full application of which the main REC has given a favourable and any conditions set out by the main REC in giving its favourable opinion.

– I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Controller.

– I understand that research records/data may be subject to inspection for audit purposes if required in future.

– I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.

Signature of the local Principal Investigator * .....

Date: (dd/mm/yyyy)

Print Name:

[illegible] Principal Investigator should sign where indicated [illegible] of the research locally

PARTS A-C NOW COMPLETE AND SHOULD BE SUBMITTED to the NRES Research Ethics Committee or NRS organisation [illegible] application

Appendix 9

A survey of cancer pain control by South West England Palliative Care Teams

Invitation letter for professionals

Invitation Letter to Palliative Care Professionals
Version 2 01/08/2005

University of BRISTOL

Dear

A Survey of Cancer Pain Control by South West England Palliative Care Teams

I am writing to invite you to take part in a research project which aims to evaluate the prevalence of unrelieved pain in cancer. This is one of a series of studies whose aim is to examine the effectiveness of the current approach to pain relief in cancer.

This study is a cross-sectional survey of patients being seen by specialist palliative care services in the South West region. I attach an information sheet which gives more details of the study and a consent form. If you are happy to participate in the study I should be grateful if you would sign the consent form and return it in the envelope provided.

I should emphasise that this is not an audit of your practice. The data are anonymised and we will not examine the pain scores or any of the clinical data according to which services or area they came from. We are interested in the larger picture to see how well our current approach to pain relief in cancer actually works in practice.

This is a timely question and the results will have important implications for ensuring that current practice is truly 'best' practice. I very much hope that you will be happy to help with this study.

Colette Reid
Research Fellow

Appendix 10

A survey of cancer pain control by South West England Palliative Care Teams

Professional consent form

University of BRISTOL

Centre Number ☐ Professional Identification Number for this trial ☐

CONSENT FORM

Title of Project: Cancer Pain Control in the South West

Name of Researcher: Dr. C Reid, Department of Palliative Medicine, University of Bristol.

Please initial box

1. I confirm that I have read and understand the Information Sheet for Health Professionals dated 25/04/05 (V3) for the above study and the Invitation Letter to Palliative Care Professionals dated 28/06/05 (V2) and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐

3. I agree to take part in the above study. ☐

Name of Professional	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 11

A survey of cancer pain control by South West England Palliative Care Teams

Ethical approval letter

South West Multi-centre Research Ethics Committee

The Lescaze Offices
Shinner's Bridge
Dartington
Devon
TQ9 6JE

Tel: 01803 861947
Fax: 01803 861914
Email: swmrec@sw-devon-ha.swest.nhs.uk

09 May 2005

Dr Colette Reid
Research Fellow in Palliative Medicine
Department of Palliative Medicine, University of Bristol
Level C, Bristol Haematology and Oncology Centre
Horfield Road
BRISTOL
BS2 8ED

Dear Dr Reid

Full title of study:	**A Survey of Cancer Pain Control by South West England Palliative Care Teams**
REC reference number:	**05/MRE06/21**
Protocol number:	**Version 2 dated 9 February 2005**

Thank you for your letter of 26 April 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by Anne Hong and Jane Maxwell.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

However, the Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. I will write to you again as soon as one Local Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application	4.0	10/02/2005	14/02/2005
Investigator CV	none given		14/02/2005
Protocol	1	09/02/2005	14/02/2005
Letter from Sponsor		31/01/2005	14/02/2005
Peer Review	Letters dated 8 June, 24 June, 14 July and 22 July 2004		14/02/2005
Indemnity letter		31/01/2005	14/02/2005
Copy of Questionnaire	v1	09/02/2005	14/02/2005
Letters of Invitation to Participants	Palliative Care Professionals v2	25/04/2005	27/04/2005
Participant Information Sheet	3 For Health Professional	25/04/2005	27/04/2005
Patient Information Sheet	v3	25/04/2005	27/04/2005
Participant Consent Form	v2	22/03/2005	31/03/2005
Participant Consent Form Professionals	v1	22/03/2005	31/03/2005
Response to Request for Further Information		29/03/2005	31/03/2005
Response to Request for Further Information		26/04/2005	27/04/2005
GP Letter	v1	18/03/2005	31/03/2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Notification of other bodies

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/MRE06/21	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely

B Lug —

John Alexander pp
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

Standard approval conditions

South West Multicentre Research Ethics Committee

List of Members for the meeting of 10 March 2005

★ **Dr John Alexander** **Chairman**	MBBS FRCA MRCS LRCP RCOG Consultant in Anaesthesia BRISTOL
🕮 ★ **Dr Harry Baumer**	MB ChB FRCP Consultant Paediatrician PLYMOUTH
🕮 ★ **Suzanne Blowey**	BSc RGN Nursing FAETC CEd Education and Development Nurse PLYMOUTH
Dr Yoav Ben-Shlomo	BSc (Hons) MBBS MRCPhys MscEpid MFPHM Senior Lecturer in Clinical Epidemiology & Hon Consultant BRISTOL
Dr Brian Cooke	MB BS LRCP MRCS FFPH Consultant in Public Health SOUTH WEST PENINSULA STRATEGIC HEALTH AUTHORITY
Mr Christopher Foy **Vice-Chairman**	MA MSc CStat Medical Statistician, R & D Support Unit GLOUCESTERSHIRE
Peter Hildrew	Lay Member BA MPA DEVON
Dr Anne Hong	FRCP FRCR Consultant Clinical Oncologist EXETER
★ **Dr Christopher Martyn**	MA D Phil FRCP Clinical Scientist/Honorary Consultant Neurologist SOUTHAMPTON
Mrs Jane Maxwell	MA (CANTAB) PGCE Lay Member GLOUCESTERSHIRE
Dr Alan Middleton	BSc MB ChB M Phil General Practitioner CORNWALL

★	
Mrs Eloise Monger	BSc (Hons) RGN ENB 100 Lecturer in Critical Care Nursing SOUTHAMPTON
Mr David Perrott	LLB (Exon); BCL (Oxon); Coif (Illinois) Lay Member EXETER
Mrs Janet Powell	JP MEd FETC Lay Member SOMERSET
🕮 ★	
Prof Alan Preece	BSc PhD FIPSM MRCSHC (PE) M Inst RP Professor of Medical Physics and Consultant Clinical Scientist BRISTOL
🕮 ★	
Dr John Reckless	DSc MD FRCP Consultant Physician and Honorary Reader in Medicine University of Bath AVON
Mrs Sally Tomlin	BPharm MBA LLM MRPharmS Pharmacist SALISBURY

Barbara Inger– MREC Committee Administrator and secretary to the meeting.

Annotation:

★	Not present at the meeting.
🕮	Submitted written comments to the meeting.

Appendix 12

A survey of cancer pain control by South West England Palliative Care Teams

Notice of substantial amendment

NHS

Central Office for Research Ethics Committees (COREC)

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available in section 5 of our Standard Operating Procedures available at www.corec.org.uk/applicants/help/docs/SOPs.doc.

Details of Chief Investigator:

Name:	Dr Colette Reid
Address:	Level C Bristol Haematology and Oncology Centre Horfield Road Bristol, BS2 8ED
Telephone:	0117 928 4591
E-mail:	Colette.reid@bristol.ac.uk
Fax:	0117 928 3865

Full title of study:	A Survey of Cancer Pain Control by South West England Palliative Care Teams
Name of main REC:	South West MREC
REC reference number:	05/MRE06/21
Date study commenced:	N/A
Protocol reference *(if applicable)*, current version and date:	Version 1 09/02/2005
Amendment number and date:	Amendment 1 26/07/2005

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC application form

Yes *No*

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes *No*

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes *No*

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold

Summary of changes

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.

Supporting scientific information should be given (or enclosed separately) where the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study.

The changes proposed have resulted from feedback about the questionnaires from both patients and professionals.
After piloting the patient questionnaire in the Bristol Haematology and Oncology Centre, we realised that we had to capture more information about the use of medication for breakthrough pain (or flares of pain). We have added two questions to the patient questionnaire in order to do this.
The professional feedback led to the addition of 3 questions and clarification of some of the original questions.
In both cases, the length of the questionnaire has not been significantly altered although the format of the professional questionnaire has been changed.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Professional Questionnaire version 1 09/02/05
Professional Questionnaire version 2 18/07/05
Patient Questionnaire version 1 09/02/05
Patient Questionnaire version 2 10/07/05

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: .....

Print name: .....

Date of submission: .....

NHS

Central Office for Research Ethics Committees (COREC)

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available in section 5 of our Standard Operating Procedures available at www.corec.org.uk/applicants/help/docs/SOPs.doc.

Details of Chief Investigator:

Name:	Dr Colette Reid
Address:	Level C Bristol Haematology and Oncology Centre Horfield Road Bristol, BS2 8ED
Telephone:	0117 928 4591
E-mail:	Colette.reid@bristol.ac.uk
Fax:	0117 928 3865

Full title of study:	A Survey of Cancer Pain Control by South West England Palliative Care Teams
Name of main REC:	South West MREC
REC reference number:	05/MRE06/21
Date study commenced:	N/A
Protocol reference *(if applicable)*, current version and date:	Version 1 09/02/2005
Amendment number and date:	Amendment 2 28/07/2005

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Professional Consent Form Version 1 22/03/05
Professional Consent Form Version 2 27/07/05
Patient Consent Form Version 2 18/03/05
Patient Consent Form Version 3 27/07/05
Patient Information Sheet Version 3 25/04/05
Patient Information Sheet Version 4 27/07/05

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: Colette M. Reid

Print name: COLETTE M. REID

Date of submission: 28th July 2005

Appendix 13

A survey of cancer pain control by South West England Palliative Care Teams

Study contact numbers for Investigator Site File

Study Information/Contact Page

A Survey of Cancer Pain Control in South West England Palliative Care Teams

Trust R&D number: 1482

MREC number: 05/MRE06/21

Sponsor Details	**Name:**	University of Bristol
	Address:	Research Enterprise and Development Senate House, Tyndall Avenue, Bristol, BS8 1TH
	Telephone:	0117 954 6966

Principal Investigator details	**Name:**	
	Address:	
	Telephone:	

Chief Investigator details	**Name:**	Dr Colette Reid
	Address:	Dept. of Palliative Medicine Level C, BHOC Horfield Rd Bristol BS2 8ED
	Telephone:	0117 928 4591

Start date: **End date:**

Appendix 14

A survey of cancer pain control by South West England Palliative Care Teams

Instructions for principal investigators

A survey of cancer pain control by South West England palliative care teams

Instructions for Principal Investigators

1. Where possible please distribute the patient information sheet to in-patients the DAY BEFORE the study, to allow patients 24 hours to decide about participating.

2. Each participating health professional should sign the study personnel page in Section 3 of the Investigator Site File.

3. Each participating health professional should sign a consent form at the start of the study day and return it to you.

4. Please ensure that all professionals understand what is required in their questionnaire at the start of the day. A definition of "opioid switch" is given on the front of their questionnaire.

5. You are provided with "patient packs" for the study. Each pack comprises a patient consent form, a patient questionnaire with a unique study number, a numbered envelope in which to place the patient questionnaire, the professional questionnaire with a matching study number, and a large envelope with the matching study number.

6. The ethics committee require that the professional should not see the patient's pain scores. Patients should place their completed questionnaires directly into the numbered envelope. If a patient requires help with completing the form, we would prefer another person e.g. a family member to assist. If this is not possible then the professional may assist the patient.

7. The consent form must be copied four times, with a copy given to the patient, and copies placed in the patient's notes, in the large envelope to be returned to Bristol and in Section 10 of the Investigator Site File.

8. The professional questionnaire needs to be completed as the patient completes their questionnaire as there will be no details to identify the patient on it. The professional questionnaire should then be placed into the large envelope along with the consent form and the envelope containing the patient questionnaire.

9. The GP letter should be sent out to the relevant general practitioner for patients seen in the community or in day care settings. Stamped envelopes are provided but you will need to address them.

Appendix 15

A survey of cancer pain control by South West England Palliative Care Teams

Subject recruitment record

Study short title	Cancer Pain Survey		
R&D Study Ref	2005.SPE.PAL.01	**Principal Investigator**	
Sponsor	University Of Bristol	**Site**	

Subject recruitment record

Initials	Gender		Consent obtained for study?		If no, consent for collection of demographic data obtained?		Patient study ID	Patient questionnaire completed?		Professional questionnaire completed?	
	Male	Female	Yes	No	Yes	No		Yes	No	Yes	No
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐

Appendix 16

A survey of cancer pain control by South West England Palliative Care Teams

Staff signature log and delegation of tasks form

Study short title	Cancer Pain Survey		
R&D Study Ref		**Principal Investigator**	
Sponsor	University of Bristol	**Site**	

Appendix 1: Site Staff Signature log & Delegation of Site Tasks

Name	Initials	Role in Study	Professional Consent signed?		Study ID	Tasks performed*	Signature	Signature of PI
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		
			Yes ☐	No ☐		1 and 2		

- **Please list study tasks** *(e.g. taking informed consent, study drug administration, taking blood samples, CRF completion etc)*

1. Obtaining informed consent

2. Completing questionnaire

Appendix 17

A survey of cancer pain control by South West England Palliative Care Teams

Trial sponsorship and insurance arrangements

University of BRISTOL

Secretary's Office, Senate House,
Tyndall Avenue, Bristol BS8 1TH
Direct line: (0117) 928 7791
Fax: (0117) 925 1558
E-mail: Ginny.Hope@bristol.ac.uk

Katharine McKenzie, BA, DPhil,
University Secretary

31 January, 2005

Our Ref: Insurance/clinical trials/CT *286* Insure confirm

(Insert details of Ethics Committee)

Ethics Application No:
Title of Research: A survey of cancer pain control by South West England Palliative care teams

The University holds the following Liability insurance policies.

Employer's Liability: Limit of Indemnity: £25M

Insurer	Policy No	Renewal Date
Royal & Sun Alliance	GA11188062	1 August 2005
ACE Europe	42UKA07016	1 August 2005

Public/Products Liability: Limit of Indemnity: £25M

Insurer	Policy No	Renewal Date
Royal & Sun Alliance	GA11188062	1 August 2005
ACE Europe	46UKC05973	1 August 2005

The Public Liability insurance includes legal liability for or arising from premises & their contents not owned by the University at which we are undertaking work in connection with our business.

Cover includes an Indemnity, at our request, to any principal against legal liability in respect of which the University would have been entitled to indemnity if the claim had been made against us.

Since this research involves a questionnaire only study, the negligible risk of injury to research subjects is considered by insurers to be covered under this Public Liability policy, rather than the university's Clinical Trials Insurance (see below)

Clinical Trials: Limit of Indemnity: £10M (max any one occurrence & period of insurance & costs inclusive)
NB Details included for information only

Insurer	Policy No	Renewal Date
Royal & Sun Alliance	GA00378442	1 August 2005

University of BRISTOL

The Clinical Trials insurance provides legal liability or non-negligent harm cover (where non-negligent harm is required for ABPI indemnified trials).

All trials are included **except** those involving:

1. More than 1500 research subjects
2. Children under the age of 5
3. Pregnant research subjects
4. Conception / contraception
5. Genetic engineering
6. Medical products manufactured by the University itself
7. Trials undertaken outside the UK

Professional Indemnity: Limit of Indemnity: £10M (maximum any one occurrence and period of Insurance)

Insurer	Policy Number	Renewal Date
Royal & Sun Alliance	60K/GA00256621	1 August 2005

Should there be any further information you require, please contact me.

Signed

Mrs V Hope ACII
Insurance Officer

Mon Jan 31 16:13:57 2005 Conditional Research sponsorship

Date: Mon, 31 Jan 2005 15:21:24 -0000
From: "Gillian Tallents, RED" <Gillian.Tallents@bristol.ac.uk>
Subject: Conditional Research sponsorship
To: Colette Reid <Colette.Reid@bristol.ac.uk>
Cc: Avril Stocks <Avril.Stocks@bristol.ac.uk>, V Hope <Ginny.Hope@bristol.ac.uk>
Message-ID: <4006125.1107184884@ored-grt.admin.bris.ac.uk>

To whom it may concern:

PROVISIONAL AGREEMENT BY THE UNIVERSITY OF BRISTOL TO ACT AS RESEARCH SPONSOR.

Title of Research: A survey of cancer pain control by South West England Palliative care teams
Chief Investigator: Dr Colette Reid

The University of Bristol hereby confirms that it will, in principle, agree to act as the research sponsor for the above project with Dr Colette Reid as Chief Investigator. This agreement is conditional on the following being in place before any participant recruitment commences:
~ NHS/Social Care approval from the relevant Research Management Office(s)
~ NHS Ethics approval.
~ Confirmation of the details of any collaborators in the research.

In order to secure FULL APPROVAL for University of Bristol sponsorship of the project, the Chief Investigator needs to send a copy of the above approval letter(s) to me as soon as possible.

Please note that NO SUBJECTS CAN BE RECRUITED TO THE STUDY UNTIL FULL APPROVAL HAS BEEN GRANTED BY THE UNIVERSITY OF BRISTOL AS RESEARCH SPONSOR.

If you have any questions regarding this email or require any further information, please do not hesitate to contact me.

Regards,
Gillian

Gillian Tallents
Research Governance Manager
University of Bristol
Research & Enterprise Development
Senate House, Tyndall Avenue, Bristol BS8 1TH
Tel: +44 (0) 117 954 6966 (ext. 46966)
Fax: +44 (0) 117 929 8383
Gillian.Tallents@bristol.ac.uk
www.bristol.ac.uk/research

Appendix 18

A survey of cancer pain control by South West England Palliative Care Teams

Letter to inform General Practitioner

GP Letter Version 1 18/03/05

University of BRISTOL

Dear Doctor

A Survey of Cancer Pain Control by South West England Palliative Care Teams

Patient's Name:

Address:

I am writing to inform you that this patient took part in a survey of cancer pain control today. This study is being conducted by the University of Bristol with the help of local palliative care teams.

He/she was asked to complete a pain questionnaire which may cause him/her to have questions about their pain or pain control. I am enclosing a copy of the questionnaire for your information.

Please contact me if you would like further details.

Yours faithfully

Dr C Reid
Research Fellow
Department of Palliative Medicine
0117 928 3336

Appendix 19

Oxycodone for cancer-related pain: meta-analysis of randomised controlled trials

Search Strategy

#1 OXYCODONE*: ME (Explode MeSH term)
#2 OXYCODONE
#3 ENDONE
#4 PROLADONE
#5 SUPEUDOL
#6 EUKADO
#7 ROXICODONE
#8 OXYCONTIN
#9 OXYNORM
#10 IMMEDIATE RELEASE OXYCODONE
#11 EUBINE
#12 ((((((((((#1 or #2) or #3) or #4) or #6) or #7) or #8) or #9) or #10) or #11)
#13 NEOPLASMS*:ME (Explode MeSH term)
#14 NEOPLASM*
#15 CANCER*
#16 (TUMOR* or TUMOUR*)
#17 (((#13 or #14) or #15) or #16)
#18 PAIN*:ME (Explode MeSH term)
#19 PAIN*
#20 (#18 or #19)
#21 ((#12 and #17) and #20)

Appendix 20

The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Study sponsor application to UBHT

Statement of Principal Investigator's Responsibilities

Name	Professor Geoffrey Hanks
Project Title	An open, randomised, parallel group study in patients with cancer pain, to compare a two-step analgesic ladder (non-opioid to oxycodone) with conventional management using a three-step approach.

As the Principal Investigator I agree to adhere to the following statements;

1. The dignity, rights, safety and well being of subjects are given priority at all times.
2. The study has UBHT Research & Development (R&D) approval prior to commencement
3. The study has appropriate Research Ethical Committee (REC) approval prior to commencement.
4. The Data Protection Officer has been informed of the study.
5. Where appropriate, permission to conduct the study has been granted by the Caldicott Guardian.
6. R&D and necessary REC approval will be gained for all protocol amendments.
7. In the event that REC and/or R&D approval be withdrawn, the study will be suspended until approval is re-instated.
8. Care staff will be adequately informed of the subjects' participation in this study.
9. The study will be conducted by myself personally and/or members of my research team.
10. Each member of the research team, including myself, who has direct involvement with research subjects and/or person-identifiable data, has a full or honorary UBHT contract.
11. Each member of the research team, including myself, is suitably qualified by education, training and experience.
12. Students and new researchers have adequate supervision, support and training.
13. Procedures are in place to ensure collection of high quality, accurate data.
14. Data will be processed and stored in accordance with the Data Protection Act 1998 and the Caldicott Principles.
15. Arrangements have been made to comply with the Health and Safety policies of the UBHT, in accordance with the Health and Safety Act 1974.
16. Serious Adverse Events will be reported to the REC and R&D Management Office.
17. Arrangements are in place for the management of financial and other resources provided for the study, including the management of any intellectual property arising.
18. Adequate and accurate records will be maintained and made available for audit as required.
19. Reports on the progress and outcomes of the work required by the R&D Management Office will be produced on time and to an acceptable standard.
20. The findings from the work will be open to critical review and disseminated appropriately.
21. Suspected research misconduct and/or fraud will be reported through appropriate systems.
22. All members of the research team are informed of their obligations in meeting the above commitments.

Signature ..... **Date** 21.VI.04

UBHT R&D PROJECT REGISTRATION FORM

The following form must be completed if your research uses **UBHT patients, staff or facilities** and submitted to the relevant research leader with a completed ethics form, UBHT Project Costing Form and Statement of Principal Investigator's Responsibilities, to receive R&D approval. Guidance for this process can be found on the UBHT R&D web site (http://www.ubht.nhs.uk/R&D) or from the R&D Office on 0117 928 3473.

Project Information

Lead researcher details *(please identify the person with overall responsibility for this project)*

Name: Professor G Hanks **Department:** Palliative Medicine **Email :** debbie.ashby@bristol.ac.uk

Type of Project: (tick as appropriate, more than one option may be selected)

Student ☐ Pilot ☒ Full ☐ Multicentre ☒

Please select the category that most accurately describes this research project:Clinical Trials

Project start date (dd/mm/yy): 01/09/04 **Project end date** (dd/mm/yy): 31/05/05 **Related website address:**

Project title *(please give the full project title here as displayed on the ethics application)*

An open, randomised, parallel group study in patients with cancer pain, to compare a two-step analgesic ladder (non-opioid to oxycodone) with conventional management using a three-step approach.

Relevance to NHS Research Priorities and Needs

Explain briefly how the project will address local and or national research priorities, indicating potential benefits to the NHS:

This project falls within the scope of the "Improving the Patient Experience" R+D programme because it's aims are to improve the management of cancer pain, both by evaluating an alternative approach to the WHO three-step analgesic ladder and by seeking to improve the communication between health professionals and patients when discussing choices in pain relief.

Is this a multidisciplinary project i.e. involving multiple professional groups? Yes

If yes, please describe the professional groups involved and how they have already or will contribute to this project:

This project will involve our clinical nurse specialists in the management of the subjects' cancer pain. We will also be collaborating with our colleagues in primary care, who will be recruiting to the trial and managing pain together with the clinical nurse specialists and study doctors.

If this project will be subject to an external review process please include the name of the reviewing organisation

This protocol has been reviewed by the Pain sub-group of the Palliative Care Clinical Studies Development Group of the NCRI. The planned definitive study is being considered for inclusion in the group's national portfolio of studies.

Please list all people who will be involved in the project at this site

Name	NHS Staff Category	UBHT Contract Type: Full	Honorary	Unknown
Prof. G. Hanks	Doctor	☐	☒	☐
Dr. C. Reid	Doctor	☐	☒	☐
Dr. Karen Forbes	Doctor	☒	☐	☐
Dr. Cath Blinman	Doctor	☐	☐	☒
Mr. James Rice	Clinical Nurse Specialist	☒	☐	☐
Ms. Gaye Senior-Smith	Clinical Nurse Specialist	☒	☐	☐

National Research Register (NRR)

This project will be submitted for inclusion in the NRR unless you indicate otherwise by placing a cross in this box. ☐

If you have put a cross in the box please indicate your reasons e.g. research has security issues, breaks confidentiality agreements with commercial sponsors or jeopardises intellectual property rights:

Intellectual Property Rights

Within UBHT Intellectual Property (IP) can be considered to be the outputs of novel research which have significant implications, both commercially and to improving patient care, and is eligible for protection to give legal recognition to it's ownership referred to as

Clinical Director: I confirm that the full implications of this project have been considered and hereby give permission for the research to be conducted as described above.

Signature of Clinical Director ..... Name (printed) CHRIS WILLIAMS ..... Date 20/7/04

UBHT Research & Effectiveness Department

Research & Effectiveness Department
Level 1, Old Building
Bristol Royal Infirmary
Bristol BS2 8HW
Tel: (0117) 928 3828 Fax: (0117) 928 3524

21 July 2004

Professor Hanks
Palliative Medicine
Bristol Haematology and Oncology Centre
Horfield Road
Bristol
BS2 8ED

Dear Professor Hanks

Re: ON/2004/1772 - An open, randomised, parallell group study in patients with cancer pain, to compare a two-step analgesic ladder with conventional management using a three-step approach

I am pleased to tell you that the above project has been approved by United Bristol Healthcare NHS Trust and can now proceed subject to full approval by the local research ethics committee.

It is essential that this project be carried out according to Good Clinical Practice and within the guidelines of the NHS Research Governance Framework for Health and Social Care (full information available on http://www.doh.gov.uk/research/rd3/nhsrandd/researchgovernance/govhome.htm or from the R&D Office). You have responsibility for ensuring that all participants sign informed consent and that the protocol agreed by the local research ethics committee is adhered to by yourself and any co-workers.

May I also remind you that as Principal Investigator you will be required to provide us with information in regard to monitoring and outcome information for this project, including a lay summary upon completion of the research. Investigators who fail to provide timely information on projects may compromise their ability to obtain Trust approval for future work.

Congratulations on initiating this research project. We wish you every success. We are keen to support good research at UBHT and are pleased that you have decided to conduct your project here.

If you need any support or information please do not hesitate to contact Debbie McPhee, R&D Information Administrator on 0117 928 3828 or by email (debbie.mcphee@ubht.swest.nhs.uk).

Yours sincerely

Maria Palmer PhD
Director of Research and Development

Appendix 21

The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Clinical Trials Authorization

MHRA
Safeguarding public health

Telephone:020 7084 2327
Facsimile:020 7084 2443
Room 12-242

Professor G Hanks
Professor of Palliative Medicine
Level C
Bristol Haematology & Oncology
Horfield Road
Bristol
BS2 8ED

Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane, London SW8 5NQ

CTA No.12893/0001/001

16 June 2004

Dear Professor Hanks

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 1031
AUTHORISATION FOR CLINICAL TRIALS INVOLVING GENERAL MEDICINAL PRODUCTS

Product: Coproxamol, Cocodamol, Morphine, Oxycodone
Protocol Number:

NOTICE OF ACCEPTANCE

I am writing to confirm that, under regulation 18(2), the Licensing Authority accepts your request to carry out a clinical trial in accordance with your letter received 30 April 2004 subject to you receiving a favourable opinion from the relevant ethics committee in accordance with regulation 15(1). You may therefore carry out the trial as notified, but I must remind you of the Authorities powers under regulation 31 to suspend or terminate a clinical trial if the conditions set out in regulation 31(1)(a) and (b) are satisfied.

The authorisation is effective from the date of this letter and may continue under this authorisation. In accordance with regulation 27, you must notify the Licensing Authority within 90 days of the conclusion of the trial, that it has ended.

Yours sincerely

Mrs S Syed
Clinical Trials Unit

Appendix 22

The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Protocol Amendment Form

Annex 2: Notification of Amendment Form

1. REVISED AMENDMENT 2

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR THE OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request:	Grounds for non acceptance / negative opinion: yes ☐ no ☐ If yes, date:
Date of start of the procedure in the CA:	Authorisation / positive opinion: yes ☐ no ☐ Date :
Competent authority/Ethics committee registration number of the trial :	

To be filled in by the applicant:
This form is common for request for authorisation from the Competent Authority and for the opinion from an Ethics Committee. Please indicate the relevant purpose in a box.

Member State in which the amendment is being submitted: U.K.

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: ☐

REQUEST FOR OPINION OF THE ETHICS COMMITTEE: ☒

NOTIFICATION FOR INFORMATION ONLY:

- to the competent authority ☐
- to the Ethics committee ☐

A 1. TRIAL IDENTIFICATION (When the amendment concerns more than one trial, repeat this form as necessary.)

EudraCT number:

Full title of the Trial:
An open, randomised, parallel group study in patients with cancer pain, to compare a two-step analgesic ladder (non-opioid to oxycodone) with conventional management using a three-step approach.

Sponsor's protocol code number :	Version	Date (yyyy-mm-dd):
ON/2003/1772	3	2004-09-17

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT

A 2. AMENDMENT IDENTIFICATION :

Amendment to 'protocol' ☐ If checked specify sponsor's amendment code number, version and date

Sponsor's protocol amendment code number :	Version	Date (yyyy-mm-dd) :
Revised Amendment 2		**2001-09-17**

Amendment to 'initial request for authorisation' ☐ If checked specify sponsor's amendment code number, version and date

Sponsor's request amendment code number :	Version	Date (yyyy-mm-dd) :

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B 1. Sponsor

Organisation: United Bristol Healthcare Trust

Name of person to contact - Given name : Maria

Name of person to contact Middle name :

Name of person to contact - Family name : Palmer

Street address : Bristol Royal Infirmary, Marlborough Street

Town / city : BRISTOL

Post code : BS2 8HW Country : U.K.

Telephone number : 0117 928 3473

Fax number : 0117 928 3524

e-mail: debbie.mcphee@ubht.swest.nhs.uk

B 2. Legal representative [1] of the sponsor in the Community for the purpose of this trial (if different from the sponsor)

Organisation:

Name of person to contact - Given name :

Name of person to contact - Middle name :

Name of person to contact - Family name :

Street address :

Town / city :

Post code : Country :

Telephone number :

Fax number :

e-mail:

[1] as stated in article 19 of Directive 2001/20/EC

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT

C. APPLICANT IDENTIFICATION, (please tick the appropriate box)

C1. Request for the competent authority ☐
- Sponsor : ☐ - Legal representative of the sponsor ☐ - Person or organisation authorised by the sponsor to make the application. In that case, complete below: ☐

C2. Request for the Ethics Committee ☒
- Sponsor : ☐ - Legal representative of the sponsor ☐ - Person or organisation authorised by the sponsor to make the application. In that case, complete below: ☐
In the case of the investigator in charge of the application, complete on next page.

Organisation:	
Name of person to contact Given name :	
Name of person to contact Middle name :	
Name of person to contact Family name :	
Street address:	
Town / city :	
Post Code:	
Telephone number:	
Fax number:	
e-mail:	

Organisation:	
Name of person to contact Given name :	
Name of person to contact Middle name :	
Name of person to contact Family name :	
Street address:	
Town / city :	
Post Code:	
Telephone number:	
Fax number:	
e-mail:	

D. TYPE OF AMENDMENT (please tick the appropriate box)

This amendment concerns mainly urgent safety measures already implemented: ☐ yes ☐ no

Reasons for the amendment:

Changes in safety or integrity of trial subjects: ☐ yes ☐ no
Changes in interpretation of scientific documents / value of the trial: ☐ yes ☐ no

Changes in quality of IMP(s): ☐ yes ☐ no

Changes in conduct or management of the trial:

Change or addition of site, principal investigator(s), co-ordinating investigator: ☐ yes ☒ no
Change of sponsor, legal representative, applicant ☐ yes ☒ no
Change in transfer of major trial related duties ☐ yes ☒ no

If yes, specify:

Other change: ☐ yes ☐ no

If yes, specify

Other case: ☐ yes ☐ no

If yes, specify:

Content of the amendment:

an amendment to information in the application form : ☐ yes ☒ no
an amendment to the protocol ☒ yes ☐ no
an amendment to other appended documents ☒ yes ☐ no

If yes, specify:

We have amended the Introductory Letter for Interview so that it refers to the approved PIS version and date. We have amended the Participant Information Sheet for Interview to state that it has been reviewed and approved by the South West MREC.

Other case : ☒ yes ☐ no

If yes, specify:

We have removed paragraph 3.1.8 in version 2 of the protocol referring to the compensation arrangements.

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT

- Investigator in charge of the application:
- Coordinating investigator (for multicentre trial) : ☒
- Principal investigator (for multicentre trial) : ☐

In the case of the Investigator, complete below

Name:	Professor Geoffrey Hanks
Street address:	Dept. of Palliative Medicine Level C Bristol Haematology and Oncology Centre Horfield Road
Town / city :	BRISTOL
Post Code:	BS2 8ED
Telephone number:	0117 928 3336
Fax number:	0117 928 3865
e-mail:	debbie.ashby@bristol.ac.uk

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT

G: LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM :

Please submit only relevant documents and / or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

- ☒ **Covering letter stating the type of amendment and the reason(s)**
- ☐ **Summary of the proposed amendment**
- ☒ **List of modified documents (identity, version, date)**
- ☒ **If applicable, pages with previous and new wording**
- ☐ **Supportive information**
- ☐ **When applicable, revised XML file and copy of initial application form with amended data highlighted**

I. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE :

I hereby confirm that/ confirm* on behalf of the sponsor* that: (*delete which is not applicable)

- the above information given on this request is correct
- the trial will be conducted according to the protocol, national regulation and the principles of good clinical practice
- it is reasonable for the proposed amendment to be undertaken.

APPLICANT of the request for the competent authority (as stated in section C1):	APPLICANT of the request for the Ethics Committee (as stated in section C2):
Date:	Date: 20. IX. 04
Signature:	Signature: G W Hanks
Print Name:	Print Name: Prof G W HANKS

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT

E. REASON FOR AMENDMENT (one or two sentences) :

This is a modification of Amendment 2 dated 13th August 2004. We were advised to make the changes by the protocol amendment committee.

F. BRIEF DESCRIPTION OF THE CHANGES :

Appendix 23

The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Letter of ethical approval

South West Multi-centre Research Ethics Committee

The Lescaze Offices
Shinner's Bridge
Dartington
Devon
TQ9 6JE

Tel: 01803 861947
Fax: 01803 861914
Email: swmrec@sw-devon-ha.swest.nhs.uk

12 October 2004

Professor Geoffrey Hanks
Dept of Palliative Medicine
Level C
Bristol Haematology and Oncology Centre
Horfield Road
Bristol
BS2 8ED

Dear Professor Hanks

Full title of study: An open, randomised, parallel group study in patients with cancer pain, to compare a two step analgesic ladder (non-opioid to oxycodone) with conventional management using a three step approach.

Amendment number: Revised Amendment 2
Amendment date: 17 September 2004

REC reference number: MREC/03/6/26
Protocol number: OXT3203

The above amendment was reviewed by the Sub-Committee of the Research Ethics Committee at the meeting held on 7 October 2004.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

- A revised Notice of Amendment form dated 20/9/04
- A copy of the current CTA
- Copy of a letter from UBHT dated 6 August 2004
- A revised protocol version 3 dated September 2004
- PIS for interview version 1 dated September 2004

Site-specific issues

It was noted as part of the review that the amendment has no implications for the suitability of local investigators, sites or facilities. You are not required to obtain any further site-specific assessment, and there is no need to inform Local Research Ethics Committees of the amendment.

Approval of host organisations

Local principal investigators or research collaborators should notify their host organisations of this amendment and check whether it affects local management approval of the research.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance (from 1 May 2004)

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: MREC/03/6/26	**Please quote this number on all correspondence**

Yours sincerely

B Inger

Barbara Inger
Committee Administrator

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

South West Multicentre Research Ethics Committee

List of Members

at

Protocol Amendment Sub-committee meeting on 7 October 2004

Dr John Alexander **Chairman**	MBBS FRCA MRCS LRCP RCOG Consultant in Anaesthesia and Pain Management BRISTOL
Prof Alan Preece	BSc PhD FIPSM MRCSHC (PE) M Inst RP Professor of Medical Physics and Consultant Clinical Scientist BRISTOL
Mr Christopher Foy	MA MSc CStat Medical Statistician, R & D Support Unit GLOUCESTERSHIRE

Barbara Inger

MREC Administrator & Secretary to the Meeting

Annotation:

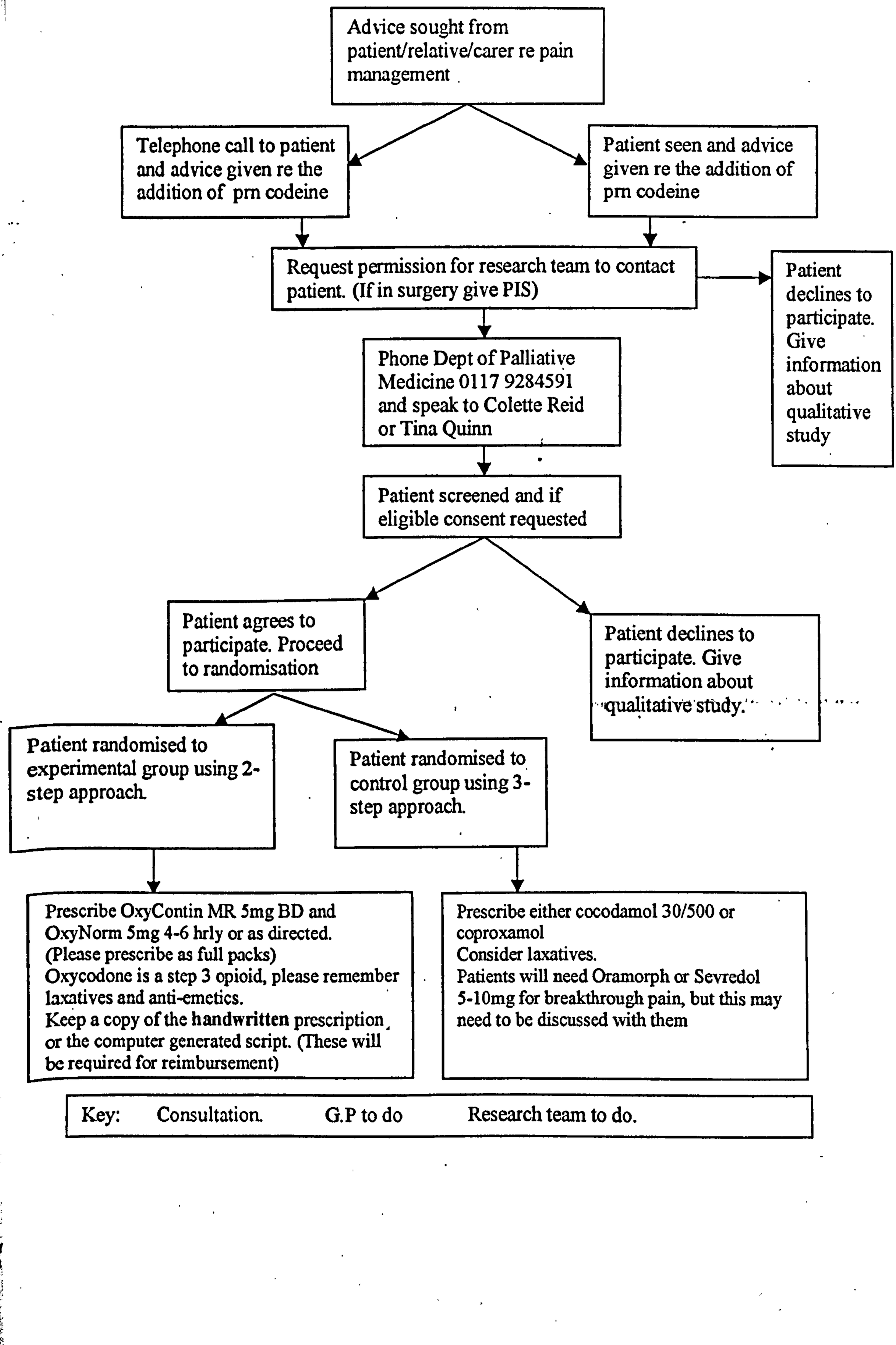
★ Not present at the meeting on 7 October 2004.
🕮 Submitted written comments to the meeting

Appendix 24

The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Flow diagram for general practitioners

Potential Recruits:
Patients with uncontrolled cancer pain only taking paracetamol or a non-steroidal anti-inflammatory drug.



Key: Consultation. G.P to do Research team to do.

Appendix 25

The 2-step study: a pilot study for a randomised controlled trial of a two-step versus a three-step approach in the management of cancer-related pain

Brief Pain Inventory

[redacted] **Protocol:** [redacted]

Investigator Number | Site Number | Patient Number | Visit Date (day / month / 20 year)

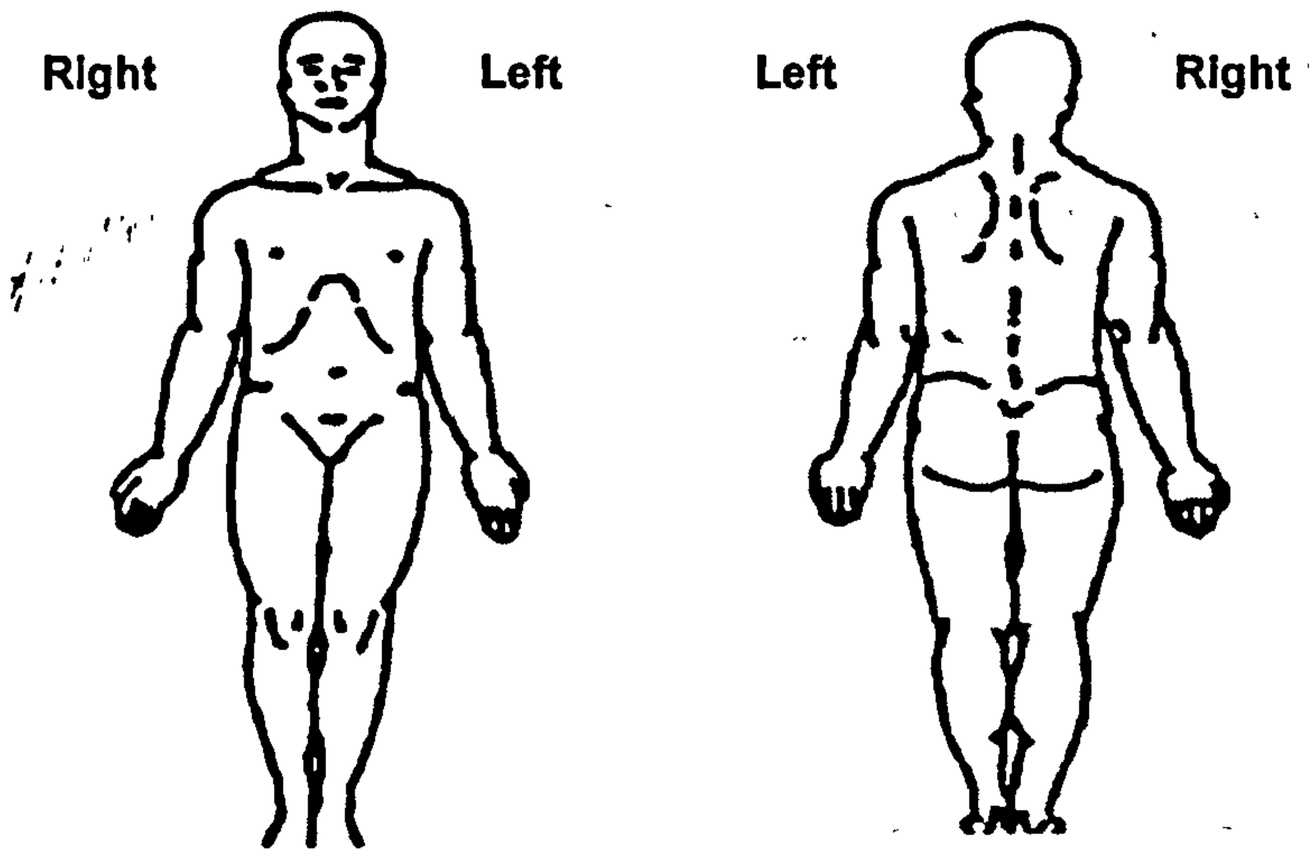
STUDY ENTRY (DAY 0)

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches).
Have you had pain other than these everyday kinds of pain today? (circle one)

   1. YES 2. NO

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours.

No Pain	0	1	2	3	4	5	6	7	8	9	10	Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its LEAST in the last 24 hours.

No Pain	0	1	2	3	4	5	6	7	8	9	10	Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the AVERAGE.

No Pain	0	1	2	3	4	5	6	7	8	9	10	Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

No Pain	0	1	2	3	4	5	6	7	8	9	10	Pain as bad as you can imagine

ALL ALTERATIONS MUST BE SIGNED AND DATED

Investigator Number | Site Number | Patient Number | Visit Date

day | month | 2 0 year

STUDY ENTRY (DAY 0)

Brief Pain Inventory (Short Form)

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much RELIEF you have received.

No Relief	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

B. Mood

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

C. Walking Ability

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

D. Normal Work (includes both work outside the home and housework)

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

E. Relations with other people

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

F. Sleep

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

G. Enjoyment of life

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely Interferes

Investigator/Co-Investigator's Signature _____ day | month | 2 0 year

ALL ALTERATIONS MUST BE SIGNED AND DATED

Appendix 26

A qualitative study to explore the views of patients considering morphine for relief of pain caused by cancer

Topic guide

A study to explore attitudes and beliefs influencing the decision to commence opioid analgesia in patients with cancer-related pain

Topic Guide for Interviews

Introduction

The researcher will confirm consent

The researcher will remind the participant that of the aim of the interview is to discuss the choice made by the participant about entering a trial which may or may not have been because one of the treatment options was a strong painkiller like morphine.
The researcher will then ask permission to discuss the participant's illness.
The participant will be asked tell the researcher about their illness (which will allow the researcher to use the appropriate terminology for that individual during the rest of the interview).

Question: e.g. "can you tell me about your illness?"

Pain History

The researcher will try to establish what coping mechanisms the participant uses and the impact of the pain on the participant.

Question: e.g. "Can you tell me about your pain?"
"Can you tell me how your pain affects you?"

Recollection of the consultation at which opioids were offered

(This will be the consultation at which the trial was discussed)

The researcher will encourage the participant to describe their recollections of this consultation and their emotions around this consultation.
The researcher will explore what the patient understood when the drug name oxycodone was mentioned.

Question: e.g. "I'd like to talk now about the appointment when the trial was discussed with you, when the team looking after you explained that an option for your pain was a strong painkiller like morphine. Can you tell me how you felt then?"

"What did you think when the drug name oxycodone was mentioned?"

Exploration of associations with oxycodone/painkillers like morphine

The researcher will ask what the participant's opinions are about opioids and possible sources of these e.g. media, health professionals, family members.

Questions: e.g. "what do you think when you hear the drug name morphine?"
"have you ever discussed using morphine with anyone else?"

Flexibility of decision to commence or delay oxycodone/painkillers like morphine

The researcher will try to establish whether decisions about commencing opioid painkillers hold firm over a short period of time.

Question: e.g. "how do you feel about this now?"
"have you had any more thoughts about your decision?"

Influence of others on the decision

If appropriate, the researcher will ask about other people who may have influenced the decision e.g. carers, family or professionals.

Question: e.g. "did you consider anyone else when you made you decision?"

If appropriate, the researcher may follow on with a question about the effect of the second step of the analgesic ladder. There will be flexibility in the words used to describe the painkiller, depending on the drug names that the participant has been using.

Question: e.g. "How would you feel if there was no option other than oxycodone for your pain?"

"How would you feel if there was no option other than morphine for your pain?"

Appendix 27

A qualitative study to explore the views of patients considering morphine for relief of pain caused by cancer

Patient information sheet

Participant Information Sheet Interview
V.2 September 2004

University of BRISTOL

Department of Palliative Medicine
Bristol Haematology & Oncology Centre
Horfield Road
Bristol BS2 8ED
Fax: +44 (0)117 928 3865

G W Hanks, DSc (Med), BSc, MB, FRCP, FRCPE, FFPM
Professor of Palliative Medicine
Tel: +44 (0)117 928 3336 Email: Debbie.Ashby@bristol.ac.uk

K Forbes, MB, FRCP
Consultant and Macmillan Senior Lecturer in Palliative Medicine
Tel: +44 (0)117 928 3507 Email: K.Forbes@bristol.ac.uk

Dear

Choices about pain relief

(A study to explore attitudes and beliefs influencing the decision to commence opioid analgesia in patients with cancer-related pain.)

You are being invited to take part in a research study. This letter is to explain the study to you, why it is being done and what it will involve. Please take time to read this and show it to others if you wish. Please ask if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

Some people become anxious the first time they are offered morphine (or a strong painkiller like morphine) for their pain. Often they decide not to try it. I would like to find out more about the reasons why people choose either to take or not to take morphine. This is part of a larger study looking at improving the management of cancer pain.

Why have I been chosen?

I want to talk to people with cancer pain who have recently been offered morphine (or a strong painkiller like morphine). I want to talk to them whether or not they have chosen to try it.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide not to take part it will not affect your treatment or care in any way. Whatever you decide, I would be grateful if you would let me know by returning the enclosed form in the pre-paid envelope. However, if I do not receive your form I will assume that you do not want to take part.

What will happen to me if I take part?

I will telephone you to arrange a convenient time and place to meet. This can be at your home if you wish. I will explain to you the purpose of the study and ask you to sign a consent form. I will then ask you some questions about the visit to the doctors when you were offered a strong painkiller like morphine. I

E J Chambers, MB, FRCR, FRCP, Honorary Senior Lecturer in Clinical Oncology and Palliative Medicine
J Skyes, MB, FRCP, Honorary Senior Lecturer in Palliative Medicine
J Gilbert, MB, FRCP, Honorary Senior Lecturer in Palliative Medicine
E Thompson, BA(Oxon), MBBS, MRCP, MFHom, Honorary Senior Lecturer in Palliative Medicine
G Tanner, BSc, MBBS, MRCGP, DGM, Honorary Senior Lecturer in Palliative Medicine

will record our conversation using a tape-recorder. Our conversation should not last longer than an hour.
I will ask you for your consent to the storage of the cassettes and the typed version of our conversation, called the transcript. These will be stored in a locked filing cabinet in a locked office. I will allocate you a study number, so your name will not appear on the outside of the cassette, nor will any other details about you.
I will also seek your permission for using anonymised quotes in my report of the study and in any scientific papers I may write about the study. You will never be identified in anything we write or say about the study.

After listening to all the conversations I record, it may be that I come to certain conclusions about how people decide whether or not to take strong painkillers like morphine. If you would like, I will tell you about these conclusions.

What are the possible risks and disadvantages of taking part?

I will be asking you to think about the thoughts and feelings you had during the appointment when your pain control and painkillers were discussed. This may have been a difficult appointment for you, so thinking about it again may be difficult. After our conversation, if you have questions about your pain control, I can help identify a professional, such as your general practitioner, for you to talk to.

Who has approved this study?

The South West Multi-centre Research Ethics Committee has reviewed and approved this study.

What do I do now?

Thank you for considering taking part in this study. I would be grateful if you could fill in the form with your decision and then send it back to me in the pre-paid envelope.

Colette Reid
Research Fellow
Dept. of Palliative Medicine
Bristol Haematology and Oncology Centre
0117 928 3336

Appendix 28

A qualitative study to explore the views of patients considering morphine for relief of pain caused by cancer

Patient consent form

Patient Consent Form Interview V1 June 2004

Study Number:

Patient Identification Number for this trial:

University of BRISTOL

Department of Palliative Medicine
Bristol Haematology & Oncology Centre
Horfield Road
Bristol BS2 8ED
Fax: +44 (0)117 928 3865

G W Hanks, DSc (Med), BSc, MB, FRCP, FRCPE, FFPM
Professor of Palliative Medicine
Tel: +44 (0)117 928 3336 Email: Debbie.Ashby@bristol.ac.uk

K Forbes, MB, FRCP
Consultant and Macmillan Senior Lecturer in Palliative Medicine
Tel: +44 (0)117 928 3507 Email: K.Forbes@bristol.ac.uk

"Choices about pain relief"

(A study to explore attitudes and beliefs influencing the decision to commence opioid analgesia in patients with cancer-related pain.)

Name of Researcher: Colette Reid Department of Palliative Medicine, Bristol University.

Please initial box

1. I confirm that I have read and understand the information sheet dated .....(version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I am happy for the interview to be tape-recorded and then written out. ☐

4. I am happy for words I used to be quoted in reports or published papers written about this study and understand that I will not be identified from these quotes. ☐

5. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Researcher	Date	Signature

(1 for patient; 1 for researcher; 1 to be kept with hospital notes)

E J Chambers, MB, FRCR, FRCP, Honorary Senior Lecturer in Clinical Oncology and Palliative Medicine
J Skyes, MB, FRCP, Honorary Senior Lecturer in Palliative Medicine
J Gilbert, MB, FRCP, Honorary Senior Lecturer in Palliative Medicine
E Thompson, BA(Oxon), MBBS, MRCP, MFHom, Honorary Senior Lecturer in Palliative Medicine
G Tanner, BSc, MBBS, MRCGP, DGM, Honorary Senior Lecturer in Palliative Medicine